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(57) Abstract

The present invention relates to novel genes from *S. aureus* and the polypeptides they encode. Also provided are vectors, host cells, antibodies and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of *S. aureus* polypeptide activity. The invention additionally relates to diagnostic methods for detecting *Staphylococcus* nucleic acids, polypeptides and antibodies in a biological sample. The present invention further relates to novel vaccines for the prevention or attenuation of infection by *Staphylococcus*.

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Staphylococcus aureus genes and polypeptides.

Field of the Invention

The present invention relates to novel *Staphylococcus aureus* genes (*S. aureus*) nucleic acids and polypeptides. Also provided are vectors, host cells and recombinant methods for producing the same. Further provided are diagnostic methods for detecting *S. aureus* using probes, primers, and antibodies to the *S. aureus* nucleic acids and polypeptides of the present invention. The invention further relates to screening methods for identifying agonists and antagonists of *S. aureus* polypeptide activity and to vaccines using *S. aureus* nucleic acids and polypeptides.

Background of the Invention

The genus *Staphylococcus* includes at least 20 distinct species. (For a review see Novick, R. P., The *Staphylococcus* as a Molecular Genetic System in MOLECULAR BIOLOGY OF THE *STAPHYLOCOCCI*, 1-37 (R. Novick, Ed., VCH Publishers, New York (1990)). Species differ from one another by 80% or more, by hybridization kinetics, whereas strains within a species are at least 90% identical by the same measure.

The species *S. aureus*, a gram-positive, facultatively aerobic, clump-forming cocci, is among the most important etiological agents of bacterial infection in humans, as discussed briefly below.

Human Health and S. aureus

Staphylococcus aureus is a ubiquitous pathogen. See, *e.g.*, Mims et al., MEDICAL MICROBIOLOGY (Mosby-Year Book Europe Limited, London, UK 1993). It is an etiological agent of a variety of conditions, ranging in severity from mild to fatal. A few of the more common conditions caused by *S. aureus* infection are burns, cellulitis, eyelid infections, food poisoning, joint infections, neonatal conjunctivitis, osteomyelitis, skin infections, surgical wound infection, scalded skin syndrome and toxic shock syndrome, some of which are described further below.

Burns: Burn wounds generally are sterile initially. However, they generally compromise physical and immune barriers to infection, cause loss of fluid and electrolytes and result in local or general physiological dysfunction. After cooling, contact with viable bacteria results in mixed colonization at the injury site. Infection may be restricted to the non-viable debris on the burn surface ("eschar"), it may progress into full skin infection and invade viable tissue below the eschar and it may reach below the skin, enter the lymphatic and blood circulation and develop into septicemia. *S. aureus* is among the most important pathogens typically found in burn wound infections. It can destroy granulation tissue and produce severe

septicemia.

Cellulitis: Cellulitis, an acute infection of the skin that expands from a typically superficial origin to spread below the cutaneous layer, most commonly is caused by *S. aureus* in conjunction with *S. pyrogenes*. Cellulitis can lead to systemic infection. In fact, cellulitis can be one aspect of synergistic bacterial gangrene. This condition typically is caused by a mixture of *S. aureus* and microaerophilic *Streptococci*. It causes necrosis and treatment is limited to excision of the necrotic tissue. The condition often is fatal.

Eyelid infections: *S. aureus* is the cause of styes and of "sticky eye" in neonates, among other eye infections. Typically such infections are limited to the surface of the eye, and may occasionally penetrate the surface with more severe consequences.

Food poisoning: Some strains of *S. aureus* produce one or more of five serologically distinct, heat and acid stable enterotoxins that are not destroyed by digestive process of the stomach and small intestine (enterotoxins A-E). Ingestion of the toxin, in sufficient quantities, typically results in severe vomiting, but not diarrhea. The effect does not require viable bacteria. Although the toxins are known, their mechanism of action is not understood.

Joint infections: *S. aureus* infects bone joints causing diseases such osteomyelitis. See, *e.g.*, R. Cunningham et al., (1996) J. Med. Microbiol. 44:157-164.

Osteomyelitis: *S. aureus* is the most common causative agent of haematogenous osteomyelitis. The disease tends to occur in children and adolescents more than adults and it is associated with non-penetrating injuries to bones. Infection typically occurs in the long end of growing bone, hence its occurrence in physically immature populations. Most often, infection is localized in the vicinity of sprouting capillary loops adjacent to epiphysis growth plates in the end of long, growing bones.

Skin infections: *S. aureus* is the most common pathogen of such minor skin infections as abscesses and boils. Such infections often are resolved by normal host response mechanisms, but they also can develop into severe internal infections. Recurrent infections of the nasal passages plague nasal carriers of *S. aureus*.

Surgical Wound Infections: Surgical wounds often penetrate far into the body. Infection of such wound thus poses a grave risk to the patient. *S. aureus* is the most important causative agent of infections in surgical wounds. *S. aureus* is unusually adept at invading surgical wounds; sutured wounds can be infected by far fewer *S. aureus* cells then are necessary to cause infection in normal skin. Invasion of surgical wound can lead to severe *S. aureus* septicemia. Invasion of the blood stream by *S. aureus* can lead to seeding and infection of internal organs, particularly heart valves and bone, causing systemic diseases, such as endocarditis and osteomyelitis.

Scalded Skin Syndrome: *S. aureus* is responsible for "scalded skin syndrome" (also called toxic epidermal necrosis, Ritter's disease and Lyell's disease). This diseases occurs in older children, typically in outbreaks caused by flowering of *S. aureus* strains produce exfoliation(also called scalded skin syndrome toxin). Although the bacteria initially may infect

only a minor lesion, the toxin destroys intercellular connections, spreads epidermal layers and allows the infection to penetrate the outer layer of the skin, producing the desquamation that typifies the diseases. Shedding of the outer layer of skin generally reveals normal skin below, but fluid lost in the process can produce severe injury in young children if it is not treated properly.

Toxic Shock Syndrome: Toxic shock syndrome is caused by strains of *S. aureus* that produce the so-called toxic shock syndrome toxin. The disease can be caused by *S. aureus* infection at any site, but it is too often erroneously viewed exclusively as a disease solely of women who use tampons. The disease involves toxemia and septicemia, and can be fatal.

Nocosomial Infections: In the 1984 National Nocosomial Infection Surveillance Study ("NNIS") *S. aureus* was the most prevalent agent of surgical wound infections in many hospital services, including medicine, surgery, obstetrics, pediatrics and newborns.

Other Infections: Other types of infections, risk factors, etc. involving *S. aureus* are discussed in: A. Trilla (1995) J. Chemotherapy 3:37-43; F. Espersen (1995) J. Chemotherapy 3:11-17; D.E. Craven (1995) J. Chemotherapy 3:19-28; J.D. Breen et al. (1995) Infect. Dis. Clin. North Am. 9(1):11-24 (each incorporated herein in their entireties).

Resistance to drugs of S. aureus strains

Prior to the introduction of penicillin the prognosis for patients seriously infected with *S. aureus* was unfavorable. Following the introduction of penicillin in the early 1940s even the worst *S. aureus* infections generally could be treated successfully. The emergence of penicillin-resistant strains of *S. aureus* did not take long, however. Most strains of *S. aureus* encountered in hospital infections today do not respond to penicillin; although, fortunately, this is not the case for *S. aureus* encountered in community infections.

It is well known now that penicillin-resistant strains of *S. aureus* produce a lactamase which converts penicillin to pencillinoic acid, and thereby destroys antibiotic activity. Furthermore, the lactamase gene often is propagated episomally, typically on a plasmid, and often is only one of several genes on an episomal element that, together, confer multidrug resistance.

Methicillins, introduced in the 1960s, largely overcame the problem of penicillin resistance in *S. aureus*. These compounds conserve the portions of penicillin responsible for antibiotic activity and modify or alter other portions that make penicillin a good substrate for inactivating lactamases. However, methicillin resistance has emerged in *S. aureus*, along with resistance to many other antibiotics effective against this organism, including aminoglycosides, tetracycline, chloramphenicol, macrolides and lincosamides. In fact, methicillin-resistant strains of *S. aureus* generally are multiply drug resistant.

Methicillian-resistant *S. aureus* (MRSA) has become one of the most important nosocomial pathogens worldwide and poses serious infection control problems. Today, many strains are multiresistant against virtually all antibiotics with the exception of vancomycin-type

glycopeptide antibiotics.

Recent reports that transfer of vancomycin resistance genes from enterococci to *S. aureus* has been observed in the laboratory sustain the fear that MRSA might become resistant against vancomycin, too, a situation generally considered to result in a public health disaster. MRSA owe their resistance against virtually all β-lactam antibiotics to the expression of an extra penicillin binding protein (PBP) 2a, encoded by the *mecA* gene. This additional very low affinity pbp, which is found exclusively in resistant strains, appears to be the only pbp still functioning in cell wall peptidoglycan synthesis at β-lactam concentrations high enough to saturate the normal set of *S. aureus* pbp 1-4. In 1983 it was shown by insertion mutagenesis using transposon Tn551 that several additional genes independent of *mecA* are needed to sustain the high level of methicillin resistance of MRSA. Interruption of these genes did not influence the resistance level by interfering with PBP2a expression, and were therefore called *fem* (factor essential for expression of methicillin resistance) or *aux* (auxiliary genes).

In the meantime six *fem* genes (femA- through F) have been described and the minimal number of additional *aux* genes has been estimated to be more than 10. Interference with *femA* and *femB* results in a strong reduction of methicillin resistance, back to sensitivity of strains without PBP2a. The *fem* genes are involved in specific steps of cell wall synthesis. Consequently, inactivation of *fem* encoded factors induce β-lactam hypersensitivity in already sensitive strains. Both *femA* and *femB* have been shown to be involved in peptidoglycan pentaglycine interpeptide bridge formation. FemA is responsible for the formation of glycines 2 and 3, and FemB is responsible for formation of glycines 4 and 5. *S. aureus* may be involved in the formation of a monoglycine muropeptide precursors. FemC-F influence amidation of the iso-D-glutamic acid residue of the peptidoglycan stem peptide, formation of a minor muropeptide with L-alanine instead of glycine at position 1 of the interpeptide bridge, perform a yet unknown function, or are involved in an early step of peptidoglycan precursors biosynthesis (addition of L-lysine), respectively.

Summary of the Invention

The present invention provides isolated *S. aureus* polynucleotides and polypeptides shown in Table 1 and SEQ ID NO:1 through SEQ ID NO:61. One aspect of the invention provides isolated nucleic acid molecules comprising or alternatively consisting of polynucleotides having a nucleotide sequence selected from the group consisting of: (a) a nucleotide sequence shown in Table 1; (b) a nucleotide sequence encoding any of the amino acid sequences of the polypeptides shown in Table 1; and (c) a nucleotide sequence complementary to any of the nucleotide sequences in (a) or (b). The invention further provides for fragments of the nucleic acid molecules of (a), (b) & (c) above.

Further embodiments of the invention include isolated nucleic acid molecules that comprise, or alternatively consist of, a polynucleotide having a nucleotide sequence at least

90% identical, and more preferably at least 95%, 96%, 97%, 98% or 99% identical, to any of the nucleotide sequences in (a), (b) or (c) above, or a polynucleotide which hybridizes under stringent hybridization conditions to a polynucleotide in (a), (b) or (c) above. Additional nucleic acid embodiments of the invention relate to isolated nucleic acid molecules comprising polynucleotides which encode the amino acid sequences of epitope-bearing portions of a *S. aureus* polypeptide having an amino acid sequence in (a) above.

The present invention also relates to recombinant vectors, which include the isolated nucleic acid molecules of the present invention, and to host cells containing the recombinant vectors, as well as to methods of making such vectors and host cells. The present invention further relates to the use of these vectors in the production of *S. aureus* polypeptides or peptides by recombinant techniques.

The invention further provides isolated *S. aureus* polypeptides having an amino acid sequence selected from the group consisting of an amino acid sequence of any of the polypeptides described in Table 1 or fragments thereof.

The polypeptides of the present invention also include polypeptides having an amino acid sequence with at least 70% similarity, and more preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% similarity to those described in Table 1, as well as polypeptides having an amino acid sequence at least 70% identical, more preferably at least 75% identical, and still more preferably 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to those above; as well as isolated nucleic acid molecules encoding such polypeptides.

The present invention further provides a vaccine, preferably a multi-component vaccine comprising one or more of the *S. aureus* polynucleotides or polypeptides described in Table 1, or fragments thereof, together with a pharmaceutically acceptable diluent, carrier, or excipient, wherein the *S. aureus* polypeptide(s) are present in an amount effective to elicit an immune response to members of the *Staphylococcus* genus, or at least *S. aureus*, in an animal. The *S. aureus* polypeptides of the present invention may further be combined with one or more immunogens of one or more other staphylococcal or non-staphylococcal organisms to produce a multi-component vaccine intended to elicit an immunological response against members of the *Staphylococcus* genus and, optionally, one or more non-staphylococcal organisms.

The vaccines of the present invention can be administered in a DNA form, *e.g.*, "naked" DNA, wherein the DNA encodes one or more staphylococcal polypeptides and, optionally, one or more polypeptides of a non-staphylococcal organism. The DNA encoding one or more polypeptides may be constructed such that these polypeptides are expressed as fusion proteins.

The vaccines of the present invention may also be administered as a component of a genetically engineered organism or host cell. Thus, a genetically engineered organism or host cell which expresses one or more *S. aureus* polypeptides may be administered to an animal. For example, such a genetically engineered organism or host cell may contain one or more *S. aureus* polypeptides of the present invention intracellularly, on its cell surface, or in its

periplasmic space. Further, such a genetically engineered organism or host cell may secrete one or more *S. aureus* polypeptides. The vaccines of the present invention may also be co-administered to an animal with an immune system modulator (*e.g.*, CD86 and GM-CSF).

The invention also provides a method of inducing an immunological response in an animal to one or more members of the *Staphylococcus* genus, preferably one or more isolates of the *S. aureus* species, comprising administering to the animal a vaccine as described above.

The invention further provides a method of inducing a protective immune response in an animal, sufficient to prevent, attenuate, or control an infection by members of the *Staphylococcus* genus, preferably at least *S. aureus* species, comprising administering to the animal a composition comprising one or more of the polynucleotides or polypeptides described in Table 1, or fragments thereof. Further, these polypeptides, or fragments thereof, may be conjugated to another immunogen and/or administered in admixture with an adjuvant.

The invention further relates to antibodies elicited in an animal by the administration of one or more *S. aureus* polypeptides of the present invention and to methods for producing such antibodies and fragments thereof. The invention further relates to recombinant antibodies and fragments thereof and to methods for producing such antibodies and fragments thereof.

The invention also provides diagnostic methods for detecting the expression of the polynucleotides and polypeptides of Table 1 by members of the *Staphylococcus* genus in a biological or environmental sample. One such method involves assaying for the expression of a polynucleotide encoding *S. aureus* polypeptides in a sample from an animal. This expression may be assayed either directly (*e.g.*, by assaying polypeptide levels using antibodies elicited in response to amino acid sequences described in Table 1) or indirectly (*e.g.*, by assaying for antibodies having specificity for amino acid sequences described in Table 1). The expression of polynucleotides can also be assayed by detecting the nucleic acids of Table 1. An example of such a method involves the use of the polymerase chain reaction (PCR) to amplify and detect *Staphylococcus* nucleic acid sequences.

The present invention also relates to nucleic acid probes having all or part of a nucleotide sequence described in Table 1 which are capable of hybridizing under stringent conditions to *Staphylococcus* nucleic acids. The invention further relates to a method of detecting one or more *Staphylococcus* nucleic acids in a biological sample obtained from an animal, said one or more nucleic acids encoding *Staphylococcus* polypeptides, comprising: (a) contacting the sample with one or more of the above-described nucleic acid probes, under conditions such that hybridization occurs, and (b) detecting hybridization of said one or more probes to the *Staphylococcus* nucleic acid present in the biological sample.

Detailed Description

The present invention relates to recombinant antigenic *S. aureus* polypeptides and fragments thereof. The invention also relates to methods for using these polypeptides to produce immunological responses and to confer immunological protection to disease caused by

members of the genus *Staphylococcus*. The invention further relates to nucleic acid sequences which encode antigenic *S. aureus* polypeptides and to methods for detecting *Staphylococcus* nucleic acids and polypeptides in biological samples. The invention also relates to *Staphylococcus* specific antibodies and methods for detecting such antibodies produced in a host animal.

Definitions

The following definitions are provided to clarify the subject matter which the inventors consider to be the present invention.

As used herein, the phrase "pathogenic agent" means an agent which causes a disease state or affliction in an animal. Included within this definition, for examples, are bacteria, protozoans, fungi, viruses and metazoan parasites which either produce a disease state or render an animal infected with such an organism susceptible to a disease state (*e.g.*, a secondary infection). Further included are species and strains of the genus *Staphylococcus* which produce disease states in animals.

As used herein, the term "organism" means any living biological system, including viruses, regardless of whether it is a pathogenic agent.

As used herein, the term "*Staphylococcus*" means any species or strain of bacteria which is members of the genus *Staphylococcus* regardless of whether they are known pathogenic agents.

As used herein, the phrase "one or more *S. aureus* polypeptides of the present invention" means the amino acid sequence of one or more of the *S. aureus* polypeptides disclosed in Table 1. These polypeptides may be expressed as fusion proteins wherein the *S. aureus* polypeptides of the present invention are linked to additional amino acid sequences which may be of Staphylococcal or non-Staphylococcal origin. This phrase further includes fragments of the *S. aureus* polypeptides of the present invention.

As used herein, the phrase "full-length amino acid sequence" and "full-length polypeptide" refer to an amino acid sequence or polypeptide encoded by a full-length open reading frame (ORF). For purposes of the present invention, polynucleotide ORFs in Table 1 are defined by the corresponding polypeptide sequences of Table 1 encoded by said polynucleotide. Therefore, a polynucleotide ORF is defined at the 5' end by the first base coding for the initiation codon of the corresponding polypeptide sequence of Table 1 and is defined at the 3' end by the last base of the last codon of said polypeptide sequence. As discussed below for polynucleotide fragments, the ORFs of the present invention may be claimed by a 5' and 3' position of a polynucleotide sequence of the present invention wherein the first base of said sequence is position 1.

As used herein, the phrase "truncated amino acid sequence" and "truncated polypeptide" refer to a sub-sequence of a full-length amino acid sequence or polypeptide. Several criteria may also be used to define the truncated amino acid sequence or polypeptide.

For example, a truncated polypeptide may be defined as a mature polypeptide (*e.g.*, a polypeptide which lacks a leader sequence). A truncated polypeptide may also be defined as an amino acid sequence which is a portion of a longer sequence that has been selected for ease of expression in a heterologous system but retains regions which render the polypeptide useful for use in vaccines (*e.g.*, antigenic regions which are expected to elicit a protective immune response).

Additional definitions are provided throughout the specification.

Explanation of Table 1

Table 1 lists the full length *S. aureus* polynucleotide and polypeptide sequences of the present invention. Each polynucleotide and polypeptide sequence is proceeded by a gene identifier. Each polynucleotide sequence is followed by at least one polypeptide sequence encoded by said polynucleotide. For some of the sequences of Table 1, a known biological activity and the name of the homolog with similar activity is listed after the gene sequence identifier.

Explanation of Table 2

Table 2 lists accession numbers for the closest matching sequences between the polypeptides of the present invention and those available through GenBank and GeneSeq databases. These reference numbers are the database entry numbers commonly used by those of skill in the art, who will be familar with their denominations. The descriptions of the nomenclature for GenBank are available from the National Center for Biotechnology Information. Column 1 lists the polynucleotide sequence of the present invention. Column 2 lists the accession number of a “match” gene sequence in GenBank or GeneSeq databases. Column 3 lists the description of the “match” gene sequence. Columns 4 and 5 are the high score and smallest sum probability, respectively, calculated by BLAST. Polypeptides of the present invention that do not share significant identity/similarity with any polypeptide sequences of GenBank and GeneSeq are not represented in Table 2. Polypeptides of the present invention that share significant identity/similarity with more than one of the polypeptides of GenBank and GeneSeq may be represented more than once.

Explanation of Table 3.

The *S. aureus* polypeptides of the present invention may include one or more conservative amino acid substitutions from natural mutations or human manipulation as indicated in Table 3. Changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein. Residues from the following groups, as indicated in Table 3, may be substituted for one another: Aromatic, Hydrophobic, Polar, Basic, Acidic, and Small,

Explanation of Table 4

Table 4 lists residues comprising antigenic epitopes of antigenic epitope-bearing fragments present in each of the full length *S. aureus* polypeptides described in Table 1 as predicted by the inventors using the algorithm of Jameson and Wolf, (1988) Comp. Appl. Biosci. 4:181-186. The Jameson-Wolf antigenic analysis was performed using the computer program PROTEAN (Version 3.11 for the Power MacIntosh, DNASTAR, Inc., 1228 South Park Street Madison, WI). *S. aureus* polypeptides shown in Table 1 may possess one or more antigenic epitopes comprising residues described in Table 4. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. The residues and locations shown described in Table 4 correspond to the amino acid sequences for each full length polypeptide sequence shown in Table 1 and in the Sequence Listing. Polypeptides of the present invention that do not have antigenic epitopes recognized by the Jameson-Wolf algorithm are not represented in Table 2.

Nucleic Acid Molecules

Sequenced *S. aureus* genomic DNA was obtained from the *S. aureus* strain ISP3. *S. aureus* strain ISP3, has been deposited at the American Type Culture Collection, as a convenience to those of skill in the art. The *S. aureus* strain ISP3 was deposited on 7 April 1998 at the ATCC, 10801 University Blvd. Manassas, VA 20110-2209, and given accession number 202108. As discussed elsewhere herein, polynucleotides of the present invention readily may be obtained by routine application of well known and standard procedures for cloning and sequencing DNA. A wide variety of *S. aureus* strains can be used to prepare *S. aureus* genomic DNA for cloning and for obtaining polynucleotides and polypeptides of the present invention. A wide variety of *S. aureus* strains are available to the public from recognized depository institutions, such as the American Type Culture Collection (ATCC). It is recognized that minor variations is the nucleic acid and amino acid sequence may be expected from *S. aureus* strain to strain. The present invention provides for genes, including both polynucleotides and polypeptides, of the present invention from all the *S. aureus* strains.

Unless otherwise indicated, all nucleotide sequences determined by sequencing a DNA molecule herein were determined using an automated DNA sequencer (such as the Model 373 from Applied Biosystems, Inc., Foster City, CA), and all amino acid sequences of polypeptides encoded by DNA molecules determined herein were predicted by translation of a DNA sequence determined as above. Therefore, as is known in the art for any DNA sequence determined by this automated approach, any nucleotide sequence determined herein may contain some errors. Nucleotide sequences determined by automation are typically at least about 90% identical, more typically at least about 95% to at least about 99.9% identical to the actual nucleotide sequence of the sequenced DNA molecule. The actual sequence can be more precisely determined by other approaches including manual DNA sequencing methods well known in the art. By "nucleotide sequence" of a nucleic acid molecule or polynucleotide is

intended to mean either a DNA or RNA sequence. Using the information provided herein, such as the nucleotide sequence in Table 1, a nucleic acid molecule of the present invention encoding a *S. aureus* polypeptide may be obtained using standard cloning and screening procedures, such as those for cloning DNAs using genomic DNA as starting material. *See, e.g.,* Sambrook et al. MOLECULAR CLONING: A LABORATORY MANUAL (Cold Spring Harbor, N.Y. 2nd ed. 1989); Ausubel et al., CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (John Wiley and Sons, N.Y. 1989). Illustrative of the invention, the nucleic acid molecule described in Table 1 was discovered in a DNA library derived from a *S. aureus* ISP3 genomic DNA.

TABLE 1. Nucleotide and Amino Acid Sequences of *S. aureus* Genes.

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>HGS001, fabH, 3-oxoacyl-acyl-carrier protein synthase
ATTAACTAGTCAATATTCCTACCTCTGACTTGAGTTTAAAAAGTAATCTATGTTAAATTAATACCTGGTATTAAAAATTT
TATTAAGAAGGTGTTCAACTATGAACGTGGGTATTAAAGGTTTTGGTGCATATGCGCCAGAAAAGATTATTGACAATGCC
TATTTTGAGCAATTTTTAGATACATCTGATGAATGGATTTCTAAGATGACTGGAATTAAAGAAAGACATTGGGCAGATGA
TGATCAAGATACTTCAGATTTAGCATATGAAGCAAGTTTAAAAGCAATCGCTGACGCTGGTATTCAGCCCGAAGATATAG
ATATGATAATTGTTGCCACAGCAaCTGGaGATATGCCATTTCCAACTGTCGCAAATATGTTGCAAGAACGTTTAGGGACG
GGCAAAGTTGCCTCTATGGATCAACTTGCAGCATGTTCTGGATTTATGTATTCAATGATTACAGCTAAACAATATGTTCA
ATCTGGAGATTATCATAACATTTTAGTTGTCGGTGCAGATAAATTATCTAAAATAACAGATTTAACTGACCGTTCTACTG
CAGTTCTATTTGGAGATGGTGCAGGTGCGGTTATCATCGGTGAAGTTTCAGATGGCAGAGGTATTATAAGTTATGAAATG
GGTTCTGATGGCACAGGTGGTAAACATTTATATTTAGATAAAGATACTGGTAAACTGAAAATGAATGGTCGAGAAGTATT
TAAATTTGCTGTTAGAATTATGGGTGATGCATCAACACGTGTAGTTGAAAAAGCGAATTTAACATCAGATGATATAGATT
TATTTATTCCTCATCAAGCTAATATTAGAATTATGGAATCAGCTAGAGAACGCTTAGGTATTTCAAAAGACAAAATGAGT
GTTTCTGTAAATAAATATGGAAATACTTCAGCTGCGTCAATACCTTTAAGTATCGATCAAGAATTAAAAAATGGTAAAAT
CAAAGATGATGATACAATTGTTCTTGTCGGATTCGGTGGCGGCCTAACTTGGGGCGCAATGACAATAAAATGGGGAAAAT
AGGAGGATAACGAATGAGTCAAAATAAAAGAGTAGTTATTACAGGTATGGGA

>HGS001, FabH, 3-oxoacyl-acyl-carrier protein synthase
MNVGIKGFGAYAPEKIIDNAYFEQFLDTSDEWISKMTGIKERHWADDDQDTSDLAYEASLKAIADAGIQPEDIDMIIVAT
ATGDMPFPTVANMLQERLGTGKVASMDQLAACSGFMYSMITAKQYVQSGDYHNILVVGADKLSKITDLTDRSTAVLFGDG
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>HGS002, murB, UDP-N-acetylenolpyruvoylglucosamine reductase
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>HGS002, MurB, UDP-N-acetylenolpyruvoylglucosamine reductase
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>HGS003, fabI, enoyl- acyl-carrier protein reductase
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>HGS003, FabI, enoyl- acyl-carrier protein reductase
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>HGS004, murA, UDP-N-acetylglucosamine 1-carboxyvinyltransferase
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>HGS004, MurA, UDP-N-acetylglucosamine 1-carboxyvinyltransferase
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>HGS005, rho, transcriptional terminator Rho
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>HGS005, Rho, transcriptional terminator Rho
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>HGS006, rnpA, ribonuclease P protein component
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>HGS006, RnpA, ribonuclease P protein component
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>HGS007M, dnaB, replicative DNA helicase
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>HGS007M, DnaB, replicative DNA helicase
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>HGS008, fabD, malonyl CoA-acyl carrier protein transacylase
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>HGS008, FabD, malonyl CoA-acyl carrier protein transacylase
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>HGS009, alf1, fructose-bisphosphate aldolase
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>HGS009, Alf1, fructose-bisphosphate aldolase
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>HGS014
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>HGS014

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>HGS016, murA, UDP-N-acetylglucosamine 1-carboxyvinyltransferase
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ATTAATTCAGTAAATTAATATAATGGAGGATTTCAACCATGGAAACAATTTTTGATTATAACCAAATTAA

>HGS016, MurA, UDP-N-acetylglucosamine 1-carboxyvinyltransferase
MDKIVIKGGNKLTGEVKVEGAKNAVLPILTASLLASDKPSKLVNVPALSDVETINNVLTTLNADVTYKKDENAVVVDATK
TLNEEAPYEYVSKMRASILVMGPLLARLGHAIVALPGGCAIGSRPIEQHIKGFEALGAEIHLENGNIYANAKDGLKGTSI
HLDFPSVGATQNIIMAASLAKGKTLIENAAKEPEIVDLANYINEMGGRITGAGTDTITINGVESLHGVEHAIIPDRIEAG
TLLIAGAITRGDIFVRGAIKEHMASLVYKLEEMGVELDYQEDGIRVRAEGELQPVDIKTLPHPGFPTDMQSQMMALLLTA
NGHKVVTETVFENRFMHVAEFKRMNANINVEGRSAKLEGKSQLQGAQVKATDLRAAAALILAGLVADGKTSVTELTHLDR
GYVDLHGKLKQLGADIERIND

>HGS018, dnaJ, DNA ligase
AGAAAAATGGCTCAATCGAACTAGATATTATCTTTAAATCACAAGGGCCAAAACGTTTGTTAGCGCAATTTGCACCAATT
GAAAAAAGGAGGATTAAGGGATGGCTGATTTATCGTCTCGTGTGAACGAGTTACATGATTTATTAAATCAATACAGTTAT
GAATACTATGTAGAGGATAATCCATCTGTACCAGATAGTGAATATGACAAATTACTTCATGAACTGATTAAAATAGAAGA
GGAGCATCCTGAGTATAAGACTGTAGATTCTCCAACAGTTAGAGTTGGCGGTGAAGCCCAAGCCTCTTTCAATAAAGTCA
ACCATGACACGCCAATGTTAAGTTTAGGGAATGCATTTAATGAGGATGATTTGAGAAAATTCGACCAACGCATACGTGAA
CAAATTGGCAACGTTGAATATATGTGCGAATTAAAAATTGATGGCTTAGCAGTATCATTGAAATATGTTGATGGATACTT
CGTTCAAGGTTTAACACGTGGTGATGGAACAACAGGTGAAGATATTACCGAAAATTTAAAAACAATTCATGCGATACCTT
TGAAAATGAAAGAACCATTAAATGTAGAAGTTCGTGGTGAAGCATATATGCCGAGACGTTCATTTTTACGATTAAATGAA
GAAAAAGAAAAAAATGATGAGCAGTTATTTGCAAATCCAAGAAACGCTGCTGCGGGATCATTAAGACAGTTAGATTCTAA
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AAGCATTAGATGAGTTAGATAAATTAGGTTTTACAACGAATAAAAATAGAGCGCGTGTAAATAATATCGATGGTGTTTTA
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AGATCAACAGGATGAGATGGGATTCACACAAAAATCTCCTAGATGGGCCATTGCTTATAAATTTCCAGCTGAGGAAGTAG
TAACTAAATTATTAGATATTGAATTAAGTATTGGACGAACAGGTGTAGTCACACCTACTGCTATTTTAGAACCAGTAAAA
GTRGCTGGTACAACTGTATCAAGAGCATCTTTGCACAATGAGGATTTAATTCATGACAGAGATATTCGAATTGGTGATAG
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CATATCATATGCCAACCCATTGTCCAAGTTGTGGACATGAATTAGTACGTATTGAAGGCGAAGTAGCACTTCGTTGCATT
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CAATGAAGCATCTAAATGGCTTGCATCACAAGGTGCTAAAGTTACAAGTAGCGTTACTAAAAATACAGATGTCGTTATTG
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CGCTGCTTGTGGTAACCATAAGGATGACCAGGCTGGAAAAGATA

>HGS018, DnaJ, DNA ligase
MADLSSRVNELHDLLNQYSYEYYVEDNPSVPDSEYDKLLHELIKIEEEHPEYKTVDSPTVRVGGEAQASFNKVNHDTPML
SLGNAFNEDDLRKFDQRIREQIGNVEYMCELKIDGLAVSLKYVDGYFVQGLTRGDGTTGEDITENLKTIHAIPLKMKEPL
NVEVRGEAYMPRRSFLRLNEEKEKNDEQLFANPRNAAAGSLRQLDSKLTAKRKLSVFIYSVNDFTDFNARSQSEALDELD
KLGFTTNKNRARVNNIDGVLEYIEKWTSQRESLPYDIDGIVIKVNDLDQQDEMGFTQKSPRWAIAYKFPAEEVVTKLLDI
ELSIGRTGVVTPTAILEPVKVAGTTVSRASLHNEDLIHDRDIRIGDSVVVKKAGDIIPEVVRSIPERRPEDAVTYHMPTH
CPSCGHELVRIEGEVALRCINPKCQAQLVEGLIHFVSRQAMNIDGLGTKIIQQLYQSELIKDVADIFYLTEEDLLPLDRM
GQKKVDNLLAAIQQAKDNSLENLLFGLGIRHLGVKASQVLAEKYETIDRLLTVTEAELVEIHDIGDKVAQSVVTYLENED
IRALIQKLKDKHVNMIYKGIKTSDIEGHPEFSGKTIVLTGKLHQMTRNEASKWLASQGAKVTSSVTKNTDVVIAGEDAGS
KLTKAQSLGIEIWTEQQFVDKQNELNS

>HGS019, mapM, methionine aminopeptidase
TGTCTCACTCACTTTCCAAAATACTAAAGTAACATCTTTAGTATATCAAAGAATTTTTGCTATAATAAGTTATAATTATA
TAAAAAAGGAACGGGATAAAATGATTGTAAAAACAGAAGAAGAATTACAAGCGTTAAAAGAAATTGGATACATATGCGCT
AAAGTGCGCAATACAATGCAAGCTGCAACCAAACCAGGTATCACTACGAAAGAGCTTGATAATATTGCGAAAGAGTTATT
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TGGCACATGGGATTCCAAGTAAGCGTGTCATTCGTGAAGGAGATTTAGTAAATATTGATGTATCGGCTTTGAAGAATGGC
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GATGGCATTTGAGAATGCAATTGCAAAAGTAAAACCGGGTACTAAGTTAAGTAACATTGGTAAAGCGGTGCATAATACAG
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GTACTTAATTACTTTGATCCAAAAGACAAAACATTATTAACTGAAGGTATGGTATTAGCTATTGAACCGTTTATCTCATC
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ATACGGTTATCGTGACTAAGGATGGTCCGATTTTAACGACAAAGATTGAAGAAGAATAGTTCAACATATACTAAGACTAA
AGTATGAACATCATTTAGTTCCGGAGCCTATTCATATTGGTTTCGGAACTGTTTTATAATAATTAAGAACACAATCAAT

>HGS019, MapM, methionine aminopeptidase
MIVKTEEELQALKEIGYICAKVRNTMQAATKPGITTKELDNIAKELFEEYGAISAPIHDENFPGQTCISVNEEVAHGIPS
KRVIREGDLVNIDVSALKNGYYADTGISFVVGESDDPMKQKVCDVATMAFENAIAKVKPGTKLSNIGKAVHNTARQNDLK
VIKNLTGHGVGLSLHEAPAHVLNYFDPKDKTLLTEGMVLAIEPFISSNASFVTEGKNEWAFETSDKSFVAQIEHTVIVTK
DGPILTTKIEEE

>HGS022-23-24, adt, glutamyl-tRNA amidotransferase subunit a, b, and c (operon comprising three ORFs listed below)
TATACAGTTTATATGAAATTAAAGTAGCACCTCATAAATACTTAGATTTTTAATTGGAAATTTGATACAATTTAGTGATG
AATGACTTAAAGGAGGCTTTTATTAATGACAAAAGTAACACGTGAAGAAGTTGAGCATATCGCGAATCTTGCAAGACTTC
AAATTTCTCCTGAAGAAACGGAAGAAATGGCCAACACATTAGAAAGCATTTTAGATTTTGCAAAACAAAATGATAGCGCT
GATACAGAAGGCGTTGAACCTACATATCACGTTTTAGATTTACAAAACGTTTTACGTGAAGATAAAGCAATTAAAGGTAT
TCCACAAGAATTAGCTTTGAAAAATGCCAAAGAAACAGAAGATGGACAATTTAAAGTGCCTACAATCATGAATGAGGAGG
ACGCGTAAGATGAGCATTCGCTACGAATCGGTTGAGAATTTATTAACTTTAATAAAAGACAAAAAAATCAAACCATCTGA
TGTTGTTAAAGATATATATGATGCAATTGAAGAGACTGATCCAACAATTAAGTCTTTTCTAGCGCTGGATAAAGAAAATG
CAATCAAAAAAGCGCAAGAATTGGATGAATTACAAGCAAAAGATCAAATGGATGGCAAATTATTTGGTATTCCAATGGGT
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ATCTACTGTAATGGAAAAACTACATAATGAAAATGCCGTTTTAATCGGTAAATTAAATATGGATGAGTTTGCAATGGGTG
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TCTGCAGCAGCAGTTGCAGCTGGCTTAGTACCATTTAGCTTAGGTTCAGACACAGGTGGTTCAATTAGACAACCGGCTGC
ATATTGTGGCGTTGTCGGTATGAAACCAACATACGGTCGTGTATCTCGATTTGGATTAGTTGCTTTTGCATCTTCATTAG
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TCGTCAAACCTTTCTCGTTTTGACGGAATTCGTTATGGTTATCATTCTAAAGAAGCTCATTCATTAGAAGAATTATATAA
AATGTCAAGATCTGAAGGTTTCGGTAAAGAAGTAAAACGTCGTATTTTCTTAGGTACATTTGCATTAAGTTCAGGTTACT
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GTCAAGAAAAATTTGGTACTAAAGCCGAATTGAAAAACTTAAACTCATTTAACTATGTACGTAAAGGTTTAGAATATGAA
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TGCAGATGTTAAATTAACATCTAACTGGTTAATGGGTGGCGTAAACGAATATTTAAATAAAAATCAAGTAGAATTATTAG
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TGAAGCAACACTTCTAAAATTTGTAAATGAAGCATTAGACAATAACGAACAATCAGTTGAAGATTACAAAAATGGTAAAG
GCAAAGCTATGGGCTTCTTAGTTGGTCAAATTATGAAAGCGTCTAAAGGTCAAGCTAATCCACAATTAGTAAATCAACTA
TTAAAACAAGAATTAGATAAAAGATAATTTAAATCATCAAACTATGAAGATTTAAAAAATAAACCCTTGATTGCTGACTT
AGATGCAATCGAGGGTTTATTTATATCTATAGAAGTCAAA

>HGS022, Adt, glutamyl-tRNA amidotransferase subunit a
MSIRYESVENLLTLIKDKKIKPSDVVKDIYDAIEETDPTIKSFLALDKENAIKKAQELDELQAKDQMDGKLFGIPMGIKD
NIITNGLETTCASKMLEGFVPIYESTVMEKLHNENAVLIGKLNMDEFAMGGSTETSYFKKTVNPFDHKAVPGGSSGGSAA
AVAAGLVPFSLGSDTGGSIRQPAAYCGVVGMKPTYGRVSRFGLVAFASSLDQIGPLTRNVKDNAIVLEAISGADVNDSTS
APVDDVDFTSEIGKDIKGLKVALPKEYLGEGVADDVKEAVQNAVETLKSLGAVVEEVSLPNTKFGIPSYYVIASSEASSN
LSRFDGIRYGYHSKEAHSLEELYKMSRSEGFGKEVKRRIFLGTFALSSGYYDAYYKKSQKVRTLIKNDFDKVFENYDVVV
GPTAPTTAFNLGEEIDDPLTMYANDLLTTPVNLAGLPGISVPCGQSNGRPIGLQFIGKPFDEKTLYRVAYQYETQYNLHD
VYEKL

>HGS023, Adt, glutamyl-tRNA amidotransferase subunit b
MHFETVIGLEVHVELKTDSKMFSPSPAHFGAEPNSNTNVIDLAYPGVLPVVNKRAVDWAMRAAMALNMEIATESKFDRKN
YFYPDNPKAYQISQFDQPIGENGYIDIEVDGETKRIGITRLHMEEDAGKSTHKGEYSLVDLNRQGTPLIEIVSEPDIRSP
KEAYAYLEKLRSIIQYTGVSDVKMEEGSLRCDANISLRPYGQEKFGTKAELKNLNSFNYVRKGLEYEEKRQEEELLNGGE
IGQETRRFDESTGKTILMRVKEGSDDYRYFPEPDIVPLYIDDAWKERVRQTIPELPDERKAKYVNELGLPAYDAHVLTLT
KEMSDFFESTIEHGADVKLTSNWLMGGVNEYLNKNQVELLDTKLTPENLAGMIKLIEDGTMSSKIAKKVFPELAAKGGNA
KQIMEDNGLVQISDEATLLKFVNEALDNNEQSVEDYKNGKGKAMGFLVGQIMKASKGQANPQLVNQLLKQELDKR

>HGS024, Adt, glutamyl-tRNA amidotransferase subunit c
MTKVTREEVEHIANLARLQISPEETEEMANTLESILDFAKQNDSADTEGVEPTYHVLDLQNVLREDKAIKGIPQELALKN
AKETEDGQFKVPTIMNEEDA

>HGS025, pth, peptidyl-tRNA hydrolase
CTTACTAAGCTAAAGAATAATGATAATTGATGGCAATGGCGGAAAATGGATGTTGTCATTATAATAATAAATGAAACAAT
TATGTTGGAGGTAAACACGCATGAAATGTATTGTAGGTCTAGGTAATATAGGTAAACGTTTTGAACTTACAAGACATAAT
ATCGGCTTTGAAGTCGTTGATTATATTTTAGAGAAAAATAATTTTTCATTAGATAAACAAAAGTTTAAAGGTGCATATAC
AATTGAACGAATGAACGGCGATAAAGTGTTATTTATCGAACCAATGACAATGATGAATTTGTCAGGTGAAGCAGTTGCAC
CGATTATGGATTATTACAATGTTAATCCAGAAGATTTAATTGTCTTATATGATGATTTAGATTTAGAACAAGGACAAGTT
CGCTTAAGACAAAAAGGAAGTGCGGGCGGTCACAATGGTATGAAATCAATTATTAAAATGCTTGGTACAGACCAATTTAA
ACGTATTCGTATTGGTGTGGGAAGACCAACGAATGGTATGACGGTACCTGATTATGTTTTACAACGCTTTTCAAATGATG
AAATGGTAACGATGGAAAAAGTTATCGAACACGCAGCACGCGCAATTGAAAAGTTTGTTGAAACATCACGATTTGACCAT
GTTATGAATGAATTTAATGGTGAAGTGAAATAATGACAATATTGACAACGCTTATAAAAGAAGATAATCATTTTCAAGAC
CTTAATCAGGTATTTGGACAAGCAAACACACTAGTAACTGGTCTTTCCCCGT

>HGS025, Pth, peptidyl-tRNA hydrolase
MKCIVGLGNIGKRFELTRHNIGFEVVDYILEKNNFSLDKQKFKGAYTIERMNGDKVLFIEPMTMMNLSGEAVAPIMDYYN
VNPEDLIVLYDDLDLEQGQVRLRQKGSAGGHNGMKSIIKMLGTDQFKRIRIGVGRPTNGMTVPDYVLQRFSNDEMVTMEK
VIEHAARAIEKFVETSRFDHVMNEFNGEVK

>HGS026
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GACCCAGATGTTGTAAATGATTCAGATAAATTACGTAAATATTCTAAAGAGCAAGCTGATTTACAAAAAACTGTAGATGT
TTATCGTAACTATAAAGCTAAAAAAGAAGAATTAGCTGATATTGAAGAAATGTTAAGTGAGACTGATGATAAAGAAGAAG
TAGAAATGTTAAAAGAGGAGAGTAATGGTATTAAAGCTGAACTTCCAAATCTTGAAGAAGAGCTTAAAATATTATTGATT
CCTAAAGATCCTAATGATGACAAAGACGTTATTGTAGAAATAAGAGCAGCAGCAGGTGGTGATGAGGCTGCGATTTTTGC
TGGTGATTTAATGCGTATGTATTCAAAGTATGCTGAATCACAAGGATTCAAAACTGAAATAGTAGAAGCGTCTGAAAGTG
ACCATGGTGGTTACAAAGAAATTAGTTTCTCAGTTTCTGGTAATGGCGCGTATAGTAAATTGAAATTTGAAAATGGTGCG
CACCGCGTTCAACGTGTGCCTGAAACAGAATCAGGTGGACGTATTCATACTTCAACAGCTACAGTGGCAGTTTTACCAGA

AGTTGAAGATGTAGAAATTGAAATTAGAAATGAAGATTTAAAAATCGACACGTATCGTTCAAGTGGTGCAGGTGGTCAGC
ACGTAAACACAACTGACTCTGCAGTACGTATTACCCATTTACCAACTGGTGTCATTGCAACATCTTCTGAGAAGTCTCAA
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>HGS026
VFDQLDIVEERYEQLNELLSDPDVVNDSDKLRKYSKEQADLQKTVDVYRNYKAKKEELADIEEMLSETDDKEEVEMLKEE
SNGIKAELPNLEEELKILLIPKDPNDDKDVIVEIRAAAGGDEAAIFAGDLMRMYSKYAESQGFKTEIVEASESDHGGYKE
ISFSVSGNGAYSKLKFENGAHRVQRVPETESGGRIHTSTATVAVLPEVEDVEIEIRNEDLKIDTYRSSGAGGQHVNTTDS
AVRITHLPTGVIATSSEKSQIQNREKAMKVLKARLYDMKVQEEQQKYASQRKSAVGTGDRSERIRTYNYPQSRVTDHRIG
LTLQKLGQIMEGHLEEIIDALTLSEQTDKLKELNNGEL

>HGS028
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CAGAAGTAGATGACATGGATGCTACTTGGGATTTATTACAAGAAGAATTTGATGAAGAAATGAAAGAAGACTTAGAGCAA
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AATTCTAGAGTTACATCCTGGTGCAGGTGGCACGGAGTCTCAAGATTGGGCTAATATGCTATTTAGAATGTATCAACGTT
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TATGAAAATGTTAAAGTCTAAATTATATCAATTAAAATTGGAAGAGCAGGCACGTGAAATGGCTGAAATTCGTGGCGAAC
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GAAGAAACAGGTAAGGTTGATGCAGTGATGGATGGAGACATTGGACCATTTATCGAATCATATTTAAGACAGACAATGTC
GCACGATTAATATATATTTTAAAACCGAGGCTCTAAAAGGGCGTCGGTTTTTGGTTTTTTTAAAGGTAGCTAAATAAATT
GTAAATTAGATTTTGGAATATGATTTGTTTATGAA

>HGS028
MELSEIKRNIDKYNQDLTQIRGSLDLENKETNIQEYEEMMAEPNFWDNQTKAQDIIDKNNALKAIVNGYKTLQAEVDDMD
ATWDLLQEEFDEEMKEDLEQEVINFKAKVDEYELQLLLDGPHDANNAILELHPGAGGTESQDWANMLFRMYQRYCEKKGF
KVETVDYLPGDEAGIKSVTLLIKGHNAYGYLKAEKGVHRLVRISPFDSSGRRHTSFASCDVIPDFNNDEIEIEINPDDIT
VDTFRASGAGGQHINKTESAIRITHHPSGIVVNNQNERSQIKNREAAMKMLKSKLYQLKLEEQAREMAEIRGEQKEIGWG
SQIRSYVFHPYSMVKDHRTNEETGKVDAVMDGDIGPFIESYLRQTMSHD

>HGS030, Tmk, thymidylate kinase
AATAACTGAAAATATGATAGAATTGGTAAATGAATATCTGGAAACTGGAATGATAGTTGAAGGAATTAAAAATAATAAAA
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TGAAGTTTACCATAGATTAGTAAAAGATTATGATGTCATTATGACTAGAGAACCAGGTGGTGTTCCTACTGGTGAAGAAA
TACGTAAAATTGTATTAGAAGGCAATGATATGGACATTAGAACTGAAGCAATGTTATTTGCTGCATCTAGAAGAGAACAT
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TCAAGGTTATGCTAGAGGGATTGGCGTTGAAGAAGTAAGAGCATTAAACGAATTTGCAATAAATGGATTATATCCAGACT
TGACGATTTATTTAAATGTTAGTGCTGAAGTAGGTCGCGAACGTATTATTAAAAATTCAAGAGATCAAAATAGATTAGAT
CAAGAAGATTTAAAGTTTCACGAAAAAGTAATTGAAGGTTACCAAGAAATCATTCATAATGAATCACAACGGTTCAAAAG
CGTTAATGCAGATCAACCTCTTGAAAATGTTGTTGAAGACACGTATCAAACTATCATCAAATATTTAGAAAAGATATGAT
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CAACTTGTTAAAAATAACTTTAGAGCAACAAAATTGGCAA

>HGS030, tmk, thymidylate kinase
MSAFITFEGPEGSGKTTVINEVYHRLVKDYDVIMTREPGGVPTGEEIRKIVLEGNDMDIRTEAMLFAASRREHLVLKVIP
ALKEGKVVLCDRYIDSSLAYQGYARGIGVEEVRALNEFAINGLYPDLTIYLNVSAEVGRERIIKNSRDQNRLDQEDLKFH
EKVIEGYQEIIHNESQRFKSVNADQPLENVVEDTYQTIIKYLEKI

>HGS031, PyrH, uridylate kinase
AATGTTGCTTTATTAAAATGTAAATCATTCTAATAAAACGACAACTGTGTCTTCTTTACTTGTATATGTTACATATATTC
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TATGGATAATAACATTCCGTTAACTGTTTTCTCTATTATGGAAGAAGGAAATATTAAACGTGCTGTTATGGGTGAAAAGA
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AAATCAATCGAAAGCTTATCACGTGAATTAGCTAACATCAGTG

>HGS031, pyrH, uridylate kinase
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>HGS032
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>HGS033
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>168153/168339, (operon comprising ORFs for five polypeptides listed below)

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>168153_3
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PILSQEINVVATLRLLEIIKKYNNHIKRFIFASSAAVYGDLPDLPKSDQSLILPLSPYAIDKYYGERTTLNYCSLYNIPTAVVKFFNVFG
PRQDPKSQYSGVISKMFDSFEHNKPFTFFGDGLQTRDFVYVYDVVQSVRLIMEHKDAIGHGYNIGTGTFTNLLEVYRIIGELYGKSVEHE
FKEARKGDIKHSYADISNLKALGFVPKYTVETGLKDYFNFEVDNIEEVTAKEVEMS

>168153_2
ATGGTTATATTCGCCATTGCTATCGTCATAGATTCGCCAGGAAACCCTATTTATAGTCAGGTTAGAGTTGGGAAGATGGGTAAATTAATT
AAAATATACAAATTACGTTCGATGTGCAAAAACGCAGAGAAAAACGGTGCGCAATGGGCTGATAAAGATGATGATCGTATAACAAATGTC
GGGAAGTTTATTCGTAAAACACGCATTGATGAATTACCACAACTAATTAATGTTGTTAAAGGGGAAATGAGTTTTATTGGACCACGCCCG
GAACGTCCGGAATTTGTAGAATTATTTAGTTCAGAAGTGATAGGTTTCGAGCAAAGATGTCTTGTTACACCAGGGTTAACAGGACTTGCG
CAAATTCAAGGTGGATATGACTTAACACCGCAACAAAAACTGAAATATGACATGAAATATATACATAAAGGTAGTTTAATGATGGAACTA
TATATATCAATTAGAACATTGATGGTTGTTATTACAGGGGAAGGCTCAAGGTAG

>168153_2
LDKLEEVRKSYYPIKRAIDLILSIVLLFLTLPIMVIFAIAIVIDSPGNPIYSQVRVGKMGKLIKIYKLRSMCKNAEKNGA
QWADKDDDRITNVGKFIRKTRIDELPQLINVVKGEMSFIGPRPERPEFVELFSSEVIGFEQRCLVTPGLTGLAQIQGGYD
LTPQQKLKYDMKYIHKGSLMMELYISIRTLMVVITGEGSR

>168153_1
ATGATTGAACAACTAGATGCAAGAGTTAATGTAATTATTATCGAACATTTAGTAGGTCCAATTGACTTTAAACAAGATATTTTAGCTGTC
AAAGTGTTAGCACAGTTATTCTCGAAAATTAAACCTGATGTTATCCATTTACATTCTTCCAAAGCTGGAACGGTCGGACGAATTGCGAAG
TTCATTTCGAAATCGAAAGACACACGTATAGTTTTTACTGCACATGGATGGGCTTTTACAGAGGGTGTTAAACCAGCTAAAAAATTTCTA
TATTTAGTTATCGAAAAATTAATGTCACTTATTACAGATAGCATTATTTGTGTTTCAGATTTCGATAAACAGTTAGCGTTAAAATATCGA
TTTAATCGATTGAAATTAACCACAATACATAATGGTATTGCAGATGTTCCCGCTGTTAAGCAAACGCTAAAAAGCCAATCACATAACAAT
ATTGGCGAAGTAGTTGGAATGTTGCCTAATAAACAAGATTTACAGATTAATGCCCCGACAAAGCATCAATTTGTTATGATTGCAAGATTT
GCTTATCCAAAATTGCCACAAAATCTAATCGCGGCAATAGAGATATTGAAATTACATAACAGTAATCATGCGCATTTTACATTTATAGGC
GATGGACCTACATTAAATGATTGTCAGCAACAAGTTGTACAAGCTGGGTTAGAAAATGATGTCACATTTTTGGGCAATGTCATTAATGCG
AGTCATTTATTATCACAATACGATACGTTTATTTTAATAAGTAAGCATGAAGGTTTGCCAATTAGCATTATAGAAGCTATGGCTACAGGT
TTGCCTGTTATAGCCAGTCATGTTGGCGGTATTTCAGAATTAGTAGCTGATAATGGTATATGTATGATGAACAACCAACCCGAAACTATT
GCTAAAGTCCTGGAAAAATATTTAATAGACAGTGATTACATCAAAATGAGTAATCAATCTAGAAAACGTTATTTAGAATGTTTTACTGAG
GAGAAAATGATTAAAGAAGTGGAAGACGTTTATAATGGAAAATCAACACAATAG

>168153_1
LKIIYCITKADNGGAQTHLIQLANHFCVHNDVYVIVGNHGPMIEQLDARVNVIIIEHLVGPIDFKQDILAVKVLAQLFSK
IKPDVIHLHSSKAGTVGRIAKFISKSKDTRIVFTAHGWAFTEGVKPAKKFLYLVIEKLMSLITDSIICVSDFDKQLALKY
RFNRLKLTTIHNGIADVPAVKQTLKSQSHNNIGEVVGMLPNKQDLQINAPTKHQFVMIARFAYPKLPQNLIAAIEILKLH
NSNHAHFTFIGDGPTLNDCQQQVVQAGLENDVTFLGNVINASHLLSQYDTFILISKHEGLPISIIEAMATGLPVIASHVG
GISELVADNGICMMNNQPETIAKVLEKYLIDSDYIKMSNQSRKRYLECFTEEKMIKEVEDVYNGKSTQ

>168339_1 (ORF overlaps the 3' end of 168153_1 by 20 nucleotides)
ATGGAAAATCAACACAATAGTAAATTACTAACATTGTTACTTATCGGTTTAGCGGTTTTTATTCAGCAATCTTCGGTTATTGCCGGTGTG
AATGTTTCTATAGCTGACTTTATCACATTACTAATATTAGTTTATTTACTGTTTTTCGCTAACCATTTATTAAAGGCAAATCATTTTTTA
CAGTTTTTCATTATTTTGTATACATATCGTATGATTATTACGCTTTGTTTGCTATTTTTTGATGATTTGATATTTATTACGGTTAAGGAA
GTTCTTGCATCTACAGTTAAATATGCATTTGTAGTCATTTATTTCTATTTAGGGATGATCATCTTTAAGTTAGGTAATAGCAAAAAAGTG
ATCGTTACCTCTTATATTATAAGCAGTGTGACTATAGGTCTATTTTGTATTATAGCTGGTTTGAACAAGTCCCCTTTACTAATGAAATTG
TTATATTTTGATGAAATACGTTCAAAAGGATTAATGAATGACCCTAACTATTTCGCGATGACACAGATTATTACATTGGTACTTGCTTAC
AAGTATATTCATAATTACATATTCAAGGTCCTTGCATGTGGTATTTTGCTATGGTCTTTAACTACAACGGGGTCTAAGACTGCGTTTATC
ATATTAATCGTCTTAGCCATTTATTTCTTTATTAAAAAGTTATTTAGTAGAAATGCGGTAAGTGTTGTGAGTATGTCAGTGATTATGCTG
ATATTACTTTGTTTTACCTTTTATAATATCAACTACTATTTATTCCAATTAAGCGACCTTGATGCCTTACCGTCATTAGATCGAATGGCG
TCTATTTTTGAAGAGGGCTTTGCATCATTAAATGATAGTGGGTCTGAGCGAAGTGTTGTATGGATAAATGCCATTTCAGTAATTAAATAT
ACACTAGGTTTTGGTGTCGGATTAGTGGATTATGTACATATTGGCTCGCAAATTAATGGTATTTTACTTGTTGCCCATAATACATATTTG
CAGATCTTTGCGGAATGGGGCATTTTATTCGGTGCATTATTTATCATATTTATGCTTTATTTACTGTTTGAATTATTTAGATTTAACATT
TCTGGGAAAAATGTAACAGCAATTGTTGTAATGTTGACGATGCTGATTTACTTTTTAACAGTATCATTTAATAACTCAAGATATGTCGCT
TTTATTTTAGGAATTATCGTCTTTATTGTTCAATATGAAAAGATGGAAAGGGATCGTAATGAAGAGTGA

>168339_1
MENQHNSKLLTLLLIGLAVFIQQSSVIAGVNVSIADFITLLILVYLLFFANHLLKANHFLQFFIILYTYRMIITLCLLFFDDLIFITVKE
VLASTVKYAFVVIYFYLGMIIFKLGNSKKVIVTSYIISSVTIGLFCIIAGLNKSPLLMKLLYFDEIRSKGLMNDPNYFAMTQIITLVLAY
KYIHNYIFKVLACGILLWSLTTTGSKTAFIILIVLAIYFFIKKLFSRNAVSVVSMSVIMLILLCFTFYNINYYLFQLSDLDALPSLDRMA
SIFEEGFASLNDSGSERSVVWINAISVIKYTLGFGVGLVDYVHIGSQINGILLVAHNTYLQIFAEWGILFGALFIIFMLYLLFELFRFNI
SGKNVTAIVVMLTMLIYFLTVSFNNSRYVAFILGIIVFIVQYEKMERDRNEE

>168339_2 (ORF overlaps the 3' end of 168339_1 by 35 nucleotides)
ATGAAAAGATGGAAAGGGATCGTAATGAAGAGTGATTCACTAAAAGAAAATATTATTTATCAAGGGCTATACCAATTGATTAGAACGATG
ACACCACTGATTACAATACCCATTATTTCACGTGCATTTGGTCCCAGTGGTGTGGGTATTGTTTCATTTTCTTTCAATATCGTGCAATAC
TTTTTGATGATTGCAAGTGTTGGCGTTCAGTTATATTTTAATAGAGTTATCGCGAAGTCCGTTAACGACAAACGGCAATTGTCACAGCAG
TTTTGGGATATCTTTGTCAGTAAATTATTTTTAGCGTTAACAGTTTTTGCGATGTATATGGTCGTAATTACTATATTTATTGATGATTAC
TATCTTATTTTCCTACTACAAGGAATCTATATTATAGGTGCAGCACTCGATATTTCATGGTTTTATGCTGGAACTGAAAAGTTTAAAATT
CCTAGCCTCAGTAATATTGTTGCGTCTGGTATTGTATTAAGTGTAGTTGTTATTTTTGTCAAAGATCAATCAGATTTATCATTGTATGTA
TTTACTATTGCTATTGTGACGGTATTAAACCAATTACCTTTGTTTATCTATTTAAAACGATACATTAGCTTTGTTTCGGTTAATTGGATA
CACGTCTGGCAATTGTTTCGTTCGTCATTAGCATACTTATTACCAAATGGACAGCTCAACTTATATACTAGTATTTCTTGCGTTGTTCTT
GGTTTAGTAGGTACATACCAACAAGTTGGTATCTTTTCTAACGCATTTAATATTTTAACGGTCGCAATCATAATGATTAATACATTTGAT
CTTGTAATGATTCCGCGTATTACCAAAATGTCTATCCAGCAATCACATAGTTTAACTAAAACGTTAGCTAATAATATGAATATTCAATTG
ATATTAACAATACCTATGGTCTTTGGTTTAATTGCAATTATGCCATCATTTTATTTATGGTTCTTTGGTGAGGAATTCGCATCAACTGTC
CCATTGATGACCATTTTAGCGATACTTGTATTAATCATTCCTTTAAATATGTTGATAAGCAGGCAATATTTATTAATAGTGAATAAAATA
AGATTATATAATGCGTCAATTACTATTGGTGCAGTGATAAACCTAGTATTATGTATTATTTTGATATATTTTTATGGAATTTACGGTGCT
GCTATTGCGCGTTTAATTACAGAGTTTTTCTTGCTCATTTGGCGATTTATTGATATTACTAAAATCAATGTGAAGTTGAATATTGTAAGT
ACGATTCAATGTGTCATTGCTGCTGTTATGATGTTTATTGTGCTTGGTGTGGTCAATCATTATTTGCCCCCTACAATGTACGCTACGCTG
CTATTAATTGCGATTGGTATAGTAGTTTATCTTTTATTAATGATGACTATGAAAAATCAATACGTATGGCAAATATTGAGGCATCTTCGA
CATAAAACAATTTAA

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>168339_2
MKSDSLKENIIYQGLYQLIRTMTPLITIPIISRAFGPSGVGIVSFSFNIVQYFLMIASVGVQLYFNRVIAKSVNDKRQLS
QQFWDIFVSKLFLALTVFAMYMVVITIFIDDYYLIFLLQGIYIIGAALDISWFYAGTEKFKIPSLSNIVASGIVLSVVVI
FVKDQSDLSLYVFTIAIVTVLNQLPLFIYLKRYISFVSVNWIHVWQLFRSSLAYLLPNGQLNLYTSISCVVLGLVGTYQQ
VGIFSNAFNILTVAIIMINTFDLVMIPRITKMSIQQSHSLTKTLANNMNIQLILTIPMVFGLIAIMPSFYLWFFGEEFAS
TVPLMTILAILVLIIPLNMLISRQYLLIVNKIRLYNASITIGAVINLVLCIILIYFYGIYGAAIARLITEFFLLIWRFID
ITKINVKLNIVSTIQCVIAAVMMFIVLGVVNHYLPPTMYATLLLIAIGIVVYLLLMMTMKNQYVWQILRHLRHKTI
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Nucleic acid molecules of the present invention may be in the form of RNA, such as mRNA, or in the form of DNA, including, for instance, DNA and genomic DNA obtained by cloning or produced synthetically. The DNA may be double-stranded or single-stranded. Single-stranded DNA or RNA may be the coding strand, also known as the sense strand, or it may be the non-coding strand, also referred to as the anti-sense strand.

By "isolated" polynucleotide sequence is intended a nucleic acid molecule, DNA or RNA, which has been removed from its native environment. This includes segments of DNA comprising the *S. aureus* polynucleotides of the present invention isolated from the native chromosome. These fragments include both isolated fragments consisting only of *S. aureus* DNA and fragments comprising heterologous sequences such as vector sequences or other foreign DNA. For example, recombinant DNA molecules contained in a vector are considered isolated for the purposes of the present invention which may be partially or substantially purified. Further examples of isolated DNA molecules include recombinant DNA molecules introduced and maintained in heterologous host cells or purified (partially or substantially) DNA molecules in solution. Isolated RNA molecules include *in vivo* or *in vitro* RNA transcripts of the DNA molecules of the present invention. Isolated nucleic acid molecules according to the present invention further include such molecules produced synthetically which may be partially or substantially purified the excluded RNA or heterologous DNA. Isolated nucleic acid molecules e at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 96%, 98%, 99%, or 100% pure relative to herelogous (Staphylococcus or other) (DNA or RNA) or relative to all materials and compounds other than the carrier solution. The term "isolated" does not refer to genomic or cDNA libraries, whole cell mRNA preparations, genomic DNA digests (including those gel separated by electrophoresis), whole chromosome or sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotides sequences of the present invention.

In addition, isolated nucleic acid molecules of the invention include DNA molecules which comprise a sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode a *S. aureus* polypeptides and peptides of the present invention (e.g. polypeptides of Table 1). That is, all possible DNA sequences that encode the *S. aureus* polypeptides of the present invention. This includes the genetic code and species-specific codon preferences known in the art. Thus, it would be routine for one skilled

in the art to generate the degenerate variants described above, for instance, to optimize codon expression for a particular host (e.g., change codons in the bacteria mRNA to those preferred by a mammalian or other bacterial host such as *E. coli*).

The invention further provides isolated nucleic acid molecules having the nucleotide sequence shown in Table 1 or a nucleic acid molecule having a sequence complementary to one of the above sequences. Such isolated molecules, particularly DNA molecules, are useful as probes for gene mapping and for identifying *S. aureus* in a biological sample, for instance, by PCR or Northern blot analysis. In specific embodiments, the polynucleotides of the present invention are less than 300kb, 200kb, 100kb, 50kb, 10,kb, 7.5kb, 5kb, 2.5kb, and 1kb. In another embodiment, the polynucleotides comprising the coding sequence for polypeptides of the present invention do not contain genomic flanking gene sequences or contain only genomic flanking gene sequences having regulatory control sequences for the said polynucleotides.

The present invention is further directed to nucleic acid molecules encoding portions or fragments of the nucleotide sequences described herein. Uses for the polynucleotide fragments of the present invention include probes, primers, molecular weight, markers and for expressing the polypeptide fragments of the present invention. Fragments include portions of the nucleotide sequences of Table 1, at least 10 contiguous nucleotides in length selected from any two integers, one of which representing a 5' nucleotide position and a second of which representing a 3' nucleotide position, where the first nucleotide for each nucleotide sequence in Table 1 is position 1. That is, every combination of a 5' and 3' nucleotide position that a fragment at least 10 contiguous nucleotides in length could occupy is included in the invention as an individual species. "At least" means a fragment may be 10 contiguous nucleotide bases in length or any integer between 10 and the length of an entire nucleotide sequence minus 1. Therefore, included in the invention are contiguous fragments specified by any 5' and 3' nucleotide base positions of a nucleotide sequences of Table 1 wherein the contiguous fragment is any integer between 10 and the length of an entire nucleotide sequence minus 1.

The polynucleotide fragment specified by 5' and 3' positions can be immediately envisaged using the clone description and are therefore not individually listed solely for the purpose of not unnecessarily lengthening the specifications.

Although it is particularly pointed out that each of the above described species may be included in or excluded from the present invention. The above species of polynucleotides fragments of the present invention may alternatively be described by the formula "a to b"; where "a" equals the 5" nucleotide position and "b" equals 3" nucleotide position of the polynucleotide fragment, where "a" equals an integer between 1 and the number of nucleotides of the polynucleotide sequence of the present invention minus 10, where "b" equals an integer between 10 and the number of nucleotides of the polynucleotide sequence of the present invention; and where 'a" is an integer smaller then "b" by at least 10.

Again, it is particularly pointed out that each species of the above formula may be specifically included in, or excluded from, the present invention. Further, the invention includes polynucleotides comprising sub-genuses of fragments specified by size, in nucleotides, rather than by nucleotide positions. The invention includes any fragment size, in contiguous nucleotides, selected from integers between 10 and the length of an entire nucleotide sequence minus 1. Preferred size of contiguous nucleotide fragments include 20 nucleotides, 30 nucleotides, 40 nucleotides, 50 nucleotides, 60 nucleotides, 70 nucleotides, 80 nucleotides, 90 nucleotides, 100 nucleotides, 125 nucleotides, 150 nucleotides, 175 nucleotides, 200 nucleotides. 250 nucleotides, 300 nucleotides, 350 nucleotides, 400 nucleotides, 450 nucleotides, 500 nucleotides, 550 nucleotides, 600 nucleotides, 650 nucleotides, 700 nucleotides, 750 nucleotides, 800 nucleotides, 850 nucleotides, 900 nucleotides, 950 nucleotides, 1000 nucleotides, 1050 nucleotides, 1100 nucleotides, and 1150 nucleotides. Other preferred sizes of contiguous polynucleotide fragments, which may be useful as diagnostic probes and primers, include fragment sizes representing each integer between 50-300. Larger fragments are also useful according to the present invention corresponding to most, if not all, of the polynucleotide sequences of the sequence listing or deposited clones. The preferred sizes are, of course, meant to exemplify not limit to present invention as all size fragments, representing any integer between 10 and the length of an entire nucleotide sequence minus 1 of the sequence listing or deposited clones, may be specifically included from the invention. Additional preferred nucleic acid fragment of the present invention include nucleic acid molecules encoding epitope-bearing portions of the polynucleotides (e.g., including but not limited to, nucleic acid molecules encoding epitope-bearing portions of the polynucleotides which are shown in Table 4).

In another aspect, the invention provides an isolated nucleic acid molecule comprising a polynucleotide which hybridizes under stringent hybridization conditions to a portion of a polynucleotide in a nucleic acid molecules of the invention described above, for instance, nucleotide sequences of Table 1. By "stringent hybridization conditions" is intended overnight incubation at 42°C in a solution comprising: 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C. Hybridizing polynucleotides are useful as diagnostic probes and primers as discussed above. Portions of a polynucleotide which hybridize to a nucleotide sequence in Table 1, which can be used as probes and primers, may be precisely specified by 5' and 3' base positions or by size in nucleotide bases as described above or precisely excluded in the same manner. Preferred hybridizing polynucleotdies of the present invention are those that, when labeled and used in a hybridization assay known in the art (e.g. Southern and Northern blot analysis), display the greatest signal strength with the polynucleotides of Table 1

regardless of other heterologous sequences present in equamolar amounts

The nucleic acid molecules of the present invention, which encode a *S. aureus* polypeptide, may include, but are not limited to, nucleic acid molecules encoding the full length *S. aureus* polypeptides of Table 1. Also included in the present invention are nucleic acids encoding the above full length sequences and further comprise additional sequences, such as those encoding an added secretory leader sequence, such as a pre-, or pro- or prepro- protein sequence. Further included in the present invention are nucleic acids encoding the above full length sequences and portions thereof and further comprise additional heterologous amino acid sequences encoded by nucleic acid sequences from a different source.

Also included in the present invention are nucleic acids encoding the above protein sequences together with additional, non-coding sequences, including for example, but not limited to non-coding 5' and 3' sequences. These sequences include transcribed, non-translated sequences that may play a role in transcription, and mRNA processing, for example, ribosome binding and stability of mRNA. Also included in the present invention are additional coding sequences which provide additional functionalities.

Thus, a nucleotide sequence encoding a polypeptide may be fused to a marker sequence, such as a sequence encoding a peptide which facilitates purification of the fused polypeptide. In certain preferred embodiments of this aspect of the invention, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. For instance, hexa-histidine provides for convenient purification of the fusion protein. See Gentz et al. (1989) Proc. Natl. Acad. Sci. 86:821-24. The "HA" tag is another peptide useful for purification which corresponds to an epitope derived from the influenza hemagglutinin protein. See Wilson et al. (1984) Cell 37:767. As discussed below, other such fusion proteins include the *S. aureus* fused to Fc at the N- or C-terminus.

Variant and Mutant Polynucleotides

The present invention further relates to variants of the nucleic acid molecules which encode portions, analogs or derivatives of a *S. aureus* polypeptides of Table 1, and variant polypeptides thereof including portions, analogs, and derivatives of the *S. aureus* polypeptides. Variants may occur naturally, such as a natural allelic variant. By an "allelic variant" is intended one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. See, *e.g.*, B. Lewin, Genes IV (1990). Non-naturally occurring variants may be produced using art-known mutagenesis techniques.

Such nucleic acid variants include those produced by nucleotide substitutions, deletions, or additions. The substitutions, deletions, or additions may involve one or more nucleotides. The variants may be altered in coding regions, non-coding regions, or both.

Alterations in the coding regions may produce conservative or non-conservative amino acid substitutions, deletions or additions. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of a *S. aureus* protein of the present invention or portions thereof. Also preferred in this regard are conservative substitutions.

Such polypeptide variants include those produced by amino acid substitutions, deletions or additions. The substitutions, deletions, or additions may involve one or more residues. Alterations may produce conservative or non-conservative amino acid substitutions, deletions, or additions. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of a *S. aureus* protein of the present invention or portions thereof. Also especially preferred in this regard are conservative substitutions.

The present invention also relates to recombinant vectors, which include the isolated nucleic acid molecules of the present invention, and to host cells containing the recombinant vectors, as well as to methods of making such vectors and host cells and for using them for production of *S. aureus* polypeptides or peptides by recombinant techniques.

The present application is directed to nucleic acid molecules at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleic acid sequence shown in Table 1. The above nucleic acid sequences are included irrespective of whether they encode a polypeptide having *S. aureus* activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having *S. aureus* activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having *S. aureus* activity include, *inter alia*, isolating an *S. aureus* gene or allelic variants thereof from a DNA library, and detecting *S. aureus* mRNA expression in biological or environmental samples, suspected of containing *S. aureus* by Northern Blot analysis or PCR.

The present invention is further directed to nucleic acid molecules having sequences at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequence shown in Table 1, which do, in fact, encode a polypeptide having *S. aureus* protein activity. By "a polypeptide having *S. aureus* activity" is intended polypeptides exhibiting activity similar, but not necessarily identical, to an activity of the *S. aureus* protein of the invention, as measured in a particular biological assay suitable for measuring activity of the specified protein. The biological activity of some of the polypeptides of the presents invention are listed in Table 1, after the name of the closest homolog with similar activity. The biological activities were determined using methods known in the art for the particular biological activity listed. For the remaining polypeptides of Table 1, the assays known in the art to measure the activity of the polypeptides of Table 2, sharing a high degree of identity, may be used to measure the activity

of the corresponding polypeptides of Table 1.

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 90%, 95%, 96%, 97%, 98%, or 99% identical to the nucleic acid sequences shown in Table 1 will encode a polypeptide having biological activity. In fact, since degenerate variants of these nucleotide sequences all encode the same polypeptide, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having biological activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the *S. aureus* polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted, inserted, or substituted with another nucleotide. The query sequence may be an entire sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

Other methods of determining and defining whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the presence invention can be done by using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. *See* Brutlag et al. (1990) Comp. App. Biosci. 6:237-245. In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by first converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

TABLE 2. Closest matching sequence between the polypeptides of the present invention an sequences in GenSeq and GenBank databases

Sequence ID	Antigen Accession No.	Match Gene Name	High Score	Smallest Sum Probability P (N)
		GenSeq		
HGS001	W34207	Streptomyces fabH homologue (frenolicin gene I pro...	285	3.50E-65
HGS001	W55808	Streptomyces roseofulvus frenolicin gene cluster p...	285	3.50E-65
HGS002	W20949	H. pylori cytoplasmic protein, 29zp10241orf7.	81	5.10E-12
HGS003	W48300	Staphylococcus aureus Fab I enoyl-ACP reductase.	1271	1.90E-170
HGS003	W40806	M. bovis InhA protein.	95	1.00E-29
HGS003	R23793	Stearoyl-ACP-desaturase (from clone pDES7).	157	1.60E-28
HGS003	R66290	M. tuberculosis inhA gene.	94	7.40E-28
HGS003	R66901	M. tuberculosis InhA.	94	7.40E-28
HGS003	R66292	Mycobacterium bovis InhA.	92	4.70E-19
HGS003	R63900	M. bovis InhA.	92	4.70E-19
HGS003	W16684	Lawsonia intracellularis enoyl-(acyl carrier prote...	114	1.80E-09
HGS003	W40805	M. tuberculosis InhA protein.	96	2.60E-09
HGS003	W40807	M. smegmatis InhA protein, mc2155 inhA-1.	101	9.70E-09
HGS004	W32287	Streptococcus pneumoniae MurA protein.	643	4.00E-89
HGS004	W26786	Streptococcus pneumoniae Mur A-1.	643	4.10E-89
HGS004	W27782	UDP-N-acetylglucosamine 1-carboxyvinyltransferase.	163	1.80E-15
HGS004	W27783	UDP-N-acetylglucosamine 1-carboxyvinyltransferase.	120	1.90E-12
HGS006	W36168	Staphylococcus aureus SP protein.	584	4.30E-78
HGS006	W37468	Staphylococcus aureus RNase P.	581	1.10E-77
HGS007M	W27798	Amino acid sequence of a replicative DNA heli case	5524	6e-83.2
HGS007M	R29636	pCTD ORF 1.	241.	7e-34.3
HGS008	W27814	A malonyl coenzymeA-acyl carrier protein transacyl...	365	4.70E-46
HGS008	W19629	Streptomyces venezuelae polyketide synthase.	96	2.30E-19
HGS008	W22602	Tylactone synthase ORF2 protein.	83	2.90E-18
HGS008	W22605	Tylactone synthase ORF5 protein.	95	8.90E-17

HGS008	R44431	eryA region polypeptide module #2.	88	2.30E-14
HGS008	R42452	Enzyme involved in eicosapentaenoic acid (EPA) syn...	94	5.30E-14
HGS008	R99462	Biosynthetic enzyme of icosapentaenoic acid synthase.	94	4.60E-13
HGS008	W37050	S. putrefaciens EPO biosynthesis gene cluster ORF6...	94	4.60E-13
HGS008	R44432	eryA region polypeptide module #3.	83	6.20E-13
HGS008	W22607	Platenolide synthase ORF2 protein.	80	2.20E-12
HGS014	W34454	Racillus subtilis teichoic acid polymerase.	597	2.70E-87
HGS014	W34455	Racillus subtilis teichoic acid polymerase.	597	3.10E-87
HGS014	W27744	Amino acid sequence of techoic acid biosynthesis p...	425	2.50E-53
HGS016	W32287	Streptococcus pneumoniae MurA protein.	643	4.00E-89
HGS016	W26786	Streptococcus pneumoniae Mur A-1.	643	4.10E-89
HGS016	W27782	UDP-N-acetylglucosamine 1-carboxyvinyltransferase.	163	1.80E-15
HGS016	W27783	UDP-N-acetylglucosamine 1-carboxyvinyltransferase.	120	1.90E-12
HGS018	R95648	Thermostable DNA-ligase.	833	3.00E-205
HGS018	R81473	Thermus aquaticus DNA ligase protein.	428	2.00E-201
HGS018	R15299	Thermostable T. aquaticus ligase (I).	428	7.40E-199
HGS018	R15694	Thermostable T. aquaticus ligase (II).	428	4.80E-196
HGS019	P70096	Met-aminopeptidase.	143	2.90E-35
HGS019	R90027	Methionine aminopeptidase sequence.	138	1.60E-20
HGS022	R12401	Enantioselective amidase of Rhodococcus.	405	4.70E-102
HGS022	R25320	Enantioselective amidase.	405	4.70E-102
HGS022	W14159	Rhodococcus rhodochrous amidase.	352	6.10E-63
HGS022	W17820	Pseudomonas putida amidase.	208	1.20E-62
HGS022	R12400	Enantioselective amidase of Brevibacterium.	353	2.90E-62
HGS022	R24529	Enantioselective amidase.	353	2.90E-62
HGS022	W10882	Comamonas acidovorans derived amidase enzyme.	261	4.00E-61
HGS022	R60155	Comamonas testosteroni NI 1 amidase.	306	5.30E-47
HGS022	R42839	Urea amidolyase.	243	1.40E-31
HGS022	R44504	Urea amide lyase.	224	8.60E-30
HGS026	W29380	S. pneumoniae peptide releasing factor RF-1.	593	3.30E-142
HGS028	W29380	S. pneumoniae peptide releasing factor RF-1.	218	1.70E-49
HGS031	W20646	H. pylori cytoplasmic protein, 02cp11822orf26.	291	5.70E-47

HGS031	W20147	H. pylori cytoplasmic protein, 14574201.aa.	75	1.50E-08
HGS033	W20861	H. pylori cell envelope transporter protein, 12ge1...	100	2.30E-18
HGS033	W20101	H. pylori transporter protein 11132778.aa.	100	6.10E-17
HGS033	W25671	hABC3 protein.	111	4.20E-15
HGS033	W46761	Amino acid sequence of human ATP binding cassette ...	111	4.20E-15
HGS033	W46771	Amino acid sequence of human ATP binding cassette ...	111	4.30E-15
HGS033	W42393	Bacillus thermoleovorans phosphatase (68FY5).	96	1.90E-13
HGS033	W34202	Streptomyces efflux pump protein (frenolicin gene ...	92	5.50E-12
HGS033	W55803	Streptomyces roseofulvus frenolicin gene cluster p...	92	5.50E-12
HGS033	W20224	H. pylori transporter protein, 22265691.aa.	88	7.40E-12
HGS033	W20668	H. pylori transporter protein O3ee11215orf29.	88	8.90E-12
HGS036	W20640	H. pylori transporter protein, 02ce11022orf8.	264	2.20E-33
HGS036	W34202	Streptomyces efflux pump protein (frenolicin gene ...	184	1.30E-29
HGS036	W55803	Streptomyces roseofulvus frenolicin gene cluster p...	184	1.30E-29
HGS036	W20289	H. pylori transporter protein, 24218968.aa.	201	5.50E-21
HGS036	W20711	H. pylori transporter protein, 05cp11911orf41.	148	2.10E-19
HGS036	W20101	H. pylori transporter protein 11132778.aa.	164	3.50E-19
HGS036	W20861	H. pylori cell envelope transporter protein, 12ge1...	164	4.20E-19
HGS036	W20492	H. pylori cell envelope transporter protein 433843...	148	1.60E-18
HGS036	W21019	H. pylori cell envelope transporter protein, hp5e1...	144	8.30E-16
HGS036	R71091	C. jejuni PEB1A antigen from ORF3.	136	7.90E-14
168153_3	W01619	Human uridine diphosphate galactose-4-epimerase.	128	9.80E-29
168153_3	W40383	S. glaucescens acbD protein.	105	1.10E-15
168153_3	R98529	dTDP-glucose dehydratase encoded by the acbB gene.	108	4.50E-15
168153_3	R80287	galE gene of S. lividans gal operon.	88	2.60E-13
168153_3	P70275	Sequence encoded by S.lividans gal operon galE gene.	86	5.10E-13
168153_3	R41529	S.lividans UDP-4-epimerase.	86	5.10E-13
168153_3	R32195	ADP-L-glycero-D-mannoheptose-6-epimerase protein.	82	3.40E-10
168153_2	W03997	Glucosyl IP-transferase (SpsB protein).	168	8.30E-36
168153_2	W32794	Sphingomonas genus microbe isolated SpsB protein.	168	8.30E-36
168153_2	W22173	S.thermophilus exopolysaccharide synthesis operon ...	141	2.20E-31
168153_2	W14074	S.thermophilus exopolysaccharide biosynthesis enzy...	141	2.20E-31
168153_2	P70458	Sequence of gpD encoded by segment of Xanthomonas ...	183	2.30E-30

168153_1	W22175	S.thermophilus exopolysaccharide synthesis operon ...	141	6.40E-35
168153_1	W14076	S.thermophilus exopolysaccharide biosynthesis enzy...	141	9.50E-35
168153_1	W22174	S.thermophilus exopolysaccharide synthesis operon ...	162	9.50E-30
168153_1	W14075	S.thermophilus exopolysaccharide biosynthesis enzy...	162	9.50E-30
168339_2	W27736	Putative O-antigen transporter protein.	820	5.70E-11.5
		GenBank		
HGS001	gnllPIDle1183136	similar to 3-oxoacyl- acyl-carrier protein	569	2.20E-129
HGS001	gil151943	ORF3; putative [Rhodobacter capsulatus]	404	1.40E-92
HGS001	gil2983572	(AE000723) 3-oxoacyl-[acyl-carrier-protein	311	5.10E-92
HGS001	gil1276662	beta-ketoacyl-acyl carrier protein synthase	292	3.90E-90
HGS001	gil2313291	(AE000540) beta-ketoacyl-acyl carrier protein	269	3.50E-89
HGS001	gnllPIDle1183019	similar to 3-oxoacyl- acyl-carrier protein	373	2.00E-86
HGS001	gil1143069	3-ketoacyl carrier protein synthase III	287	3.60E-86
HGS001	gil22744	beta-ketoacyl-acyl carrier protein synthase	292	1.20E-85
HGS001	gil311686	3-ketoacyl-acyl carrier protein synthase	322	3.40E-85
HGS001	gil145898	beta-ketoacyl-acyl carrier protein synthase	366	7.30E-84
HGS002	gil142833	ORF2 [Bacillus subtilis] >gnllPIDle11851...	215	2.50E-70
HGS002	gnllPIDld1019368	hypothetical protein [Synechocystis sp.]	235	8.50E-67
HGS002	gil2983165	(AE000694) UDP-N-acetylenolpyruvoylgluco...	207	1.10E-58
HGS002	gil404010	ORF2 [Bacillus licheniformis] >pirlI4022...	251	1.10E-50
HGS002	gil2688520	(AE001161) UDP-N-acetylmuramate dehydrog...	197	1.80E-42
HGS002	gil1841789	UDP-N-acetylenolpyruvylglucosamine reduc...	249	7.10E-40
HGS002	gil2983149	(AE000693) UDP-N-acetoenolpyruvoylglucos...	212	3.80E-36
HGS002	gil431730	UDP-N-acetylenolpyruvoylglucosamine redu...	119	4.50E-22
HGS002	gil1573234	UDP-N-acetylenolpyruvoylglucosamine redu...	139	6.20E-22
HGS002	gil290456	UDP-N-acetylpyruvoylglucosamine reductas...	123	2.90E-20
HGS003	gnllPIDle1183192	similar to enoyl- acyl-carrier protein r...	743	1.80E-97
HGS003	gil142010	Shows 70.2% similarity and 48.6% identit...	519	8.90E-80
HGS003	gnllPIDld1017769	enoyl-[acyl-carrier-protein] reductase [...	482	2.10E-73
HGS003	gil2313282	(AE000539) enoyl-(acyl-carrier-protein) ...	449	1.70E-71
HGS003	gil145851	envM [Escherichia coli] >gil587106 enoyl...	388	3.70E-71
HGS003	gil153955	envM protein [Salmonella typhimurium] >p...	386	2.10E-69

HGS003	gil1574591	short chain alcohol dehydrogenase homolo...	362	3.10E-68
HGS003	gil2983915	(AE000745) enoyl-[acyl-carrier-protein] ...	268	1.10E-64
HGS003	gil1053075	orf1; similar to E.coli EnvM [Proteus mi...	259	2.60E-29
HGS003	gnllPIDle1188732	(AJ003124) enoyl-ACP reductase [Petunia ...	154	2.20E-28
HGS004	gnllPIDle276830	UDP-N-acetylglucosamine 1-carboxyvinyltr...	1251	2.50E-195
HGS004	gil415662	UDP-N-acetylglucosamine 1-carboxyvinyl t...	534	1.40E-139
HGS004	gnllPIDld1010850	UDP-N-acetylglucosamine 1-carboxyvinyltr...	732	7.50E-138
HGS004	gil41344	UDP-N-acetylglucosamine 1-carboxyvinyltr...	537	2.90E-137
HGS004	gil1574635	UDP-N-acetylglucosamine enolpyruvyl tran...	536	4.70E-136
HGS004	gil146902	UDP-N-acetylglucosamine enolpyruvyl tran...	509	5.10E-134
HGS004	gil2983705	(AE000732) UDP-N-acetylglucosamine 1-car...	492	6.20E-121
HGS004	gnllPIDle229797	UDP-N-acetylglucosamine enolpyruvyl tran...	606	3.00E-119
HGS004	gil699337	UDP-N-acetyglucosamine 1-carboxyvinyl tr...	605	1.10E-118
HGS004	gil2313767	(AE000578) UDP-N-acetylglucosamine enolp...	440	1.90E-117
HGS005	gil143434	Rho Factor [Bacillus subtilis]	755	1.10E-190
HGS005	gil853769	transcriptional terminator Rho [Bacillus ...	746	1.80E-189
HGS005	gil2983405	(AE000711) transcriptional terminator Rho...	580	2.10E-154
HGS005	gil454859	The first ATG in the open reading frame ...	543	7.90E-150
HGS005	gil147607	transcription termination factor [Escheri...	592	9.40E-149
HGS005	gil49363	ho Factor [Salmonella typhimurium] >pirl...	592	1.70E-148
HGS005	gnllPIDle220353	Rho gene product [Streptomyces lividans] ...	575	4.90E-148
HGS005	gil1573263	transcription termination factor rho (rho...	575	5.40E-147
HGS005	gil49365	Rho factor [Neisseria gonorrhoeae] >pirl...	590	1.40E-146
HGS005	gil2313666	(AE000569) transcription termination fact...	547	8.10E-146
HGS006	gil580904	homologous to E.coli rnpA [Bacillus subt...	295	8.10E-37
HGS006	gnllPIDld1005777	protein component of ribonuclease P [Bac...	293	1.60E-36
HGS006	gnllPIDld1004132	RNaseP C5 subunit [Mycoplasma capricolum...	99	3.60E-22
HGS006	gil144147	rnpA [Buchnera aphidicola] >gil2827012 (...	97	3.90E-10
HGS006	gil511457	RNase P protein component [Coxiella burn...	117	2.30E-09
HGS007M	gnllPIDld1005718	replicative DNA helicase [Bacillus subti...	579	6.20E-169
HGS007M	gil3282821	(AF045058) DnaC replicative helicase [Ba...	536	3.60E-156
HGS007M	gnllPIDle321938	helicase [Rhodothermus marinus]	433	1.50E-123

HGS007M	gil2335167	(AF006675) DNA helicase [Rhodothermus ma...	271	2.90E-109
HGS007M	gnllPIDle211889	DNA-replication helicase [Odontella sine...	395	1.60E-108
HGS007M	gnllPIDle1263993	(AL022118) replicative DNA helicase DnaB...	235	3.20E-103
HGS007M	gnllPIDle244747	gene 40 [Bacteriophage SPP1] >gil529650 ...	477	4.40E-103
HGS007M	gil2983861	(AE000742) replicative DNA helicase [Aqu...	244	1.10E-102
HGS007M	gil2314528	(AE000636) replicative DNA helicase (dna...	246	7.70E-101
HGS007M	gnllPIDld1011167	replicative DNA helicase [Synechocystis ...	209	1.50E-100
HGS008	gnllPIDle1185181	malonyl CoA-acyl carrier protein transac...	560	4.30E-90
HGS008	gil1502420	malonyl-CoA:Acyl carrier protein transac...	391	1.40E-86
HGS008	gil3282803	(AF044668) malonyl CoA-acyl carrier prot...	308	2.50E-75
HGS008	gil2738154	malonyl-CoA:acyl carrier protein transac...	283	3.40E-75
HGS008	gil145887	malonyl coenzyme A-acyl carrier protein ...	304	6.30E-75
HGS008	gil1573113	malonyl coenzyme A-acyl carrier protein ...	270	7.60E-74
HGS008	gil2983416	(AE000712) malonyl-CoA:Acyl carrier prot...	213	2.70E-73
HGS008	gil840626	transacylase [Bacillus subtilis]	221	1.20E-66
HGS008	gil3150402	(AC004165) putative malonyl-CoA:Acyl car...	235	1.60E-57
HGS008	gnllPIDle1185300	pksC [Bacillus subtilis] >gnllPIDle11833...	145	4.40E-38
HGS009	gil460911	fructose-bisphosphate aldolase [Bacillus...	1169	2.10E-154
HGS009	gnllPIDle1251871	fructose-1,6-bisphosphate aldolase type ...	1121	6.70E-148
HGS009	gnllPIDld1003809	hypothetical protein [Bacillus subtilis]...	467	1.50E-110
HGS009	gil2313265	(AE000538) fructose-bisphosphate aldolas...	252	6.40E-91
HGS009	gil1673788	(AE000015) Mycoplasma pneumoniae, fructo...	238	4.60E-81
HGS009	gil1045692	fructose-bisphosphate aldolase [Mycoplas...	226	6.40E-77
HGS009	gnllPIDld1016691	Tagatose-bisphosphate aldolase GatY (EC ...	279	2.30E-75
HGS009	gil599738	unknown function [Escherichia coli] >pir...	274	2.00E-74
HGS009	gil1732204	putative aldolase [Vibrio furnissii]	277	5.00E-74
HGS009	gil606077	ORF_o286 [Escherichia coli] >gil1789526 ...	264	1.30E-73
HGS014	gil40100	rodC (tag3) polypeptide (AA 1-746) [Baci...	597	1.70E-86
HGS014	gnllPIDle1169895	tasA [Streptococcus pneumoniae]	108	4.90E-27
HGS014	gil2621425	(AE000822) teichoic acid biosynthesis pr...	142	2.00E-23
HGS014	gil2621421	(AE000822) teichoic acid biosynthesis pr...	147	5.90E-22
HGS014	gil143725	putative [Bacillus subtilis] >gnllPIDle1...	114	4.60E-19

HGS014	gi|547513	orf3 [Haemophilus influenzae] >pir|S4924...	106	5.60E-14
HGS014	gnl|PID|d1027517	(AB009477) 395aa long hypothetical prote...	79	4.20E-12
HGS014	gi|2072447	EpsJ [Lactococcus lactis cremoris]	106	5.20E-10
HGS014	gi|915199	ggaB [Bacillus subtilis] >gnl|PID|e11844...	89	8.10E-08
HGS016	gnl|PID|e276830	UDP-N-acetylglucosamine 1-carboxyvinyltr...	1251	2.50E-195
HGS016	gi|415662	UDP-N-acetylglucosamine 1-carboxyvinyl t...	534	1.40E-139
HGS016	gnl|PID|d1010850	UDP-N-acetylglucosamine 1-carboxyvinyltr...	732	7.50E-138
HGS016	gi|41344	UDP-N-acetylglucosamine 1-carboxyvinyltr...	537	2.90E-137
HGS016	gi|1574635	UDP-N-acetylglucosamine enolpyruvyl tran...	536	4.70E-136
HGS016	gi|146902	UDP-N-acetylglucosamine enolpyruvyl tran...	509	5.10E-134
HGS016	gi|2983705	(AE000732) UDP-N-acetylglucosamine 1-car...	492	6.20E-121
HGS016	gnl|PID|e229797	UDP-N-acetylglucosamine enolpyruvyl tran...	606	3.00E-119
HGS016	gi|699337	UDP-N-acetyglucosamine 1-carboxyvinyl tr...	605	1.10E-118
HGS016	gi|2313767	(AE000578) UDP-N-acetylglucosamine enolp...	440	1.90E-117
HGS018	gnl|PID|e1182642	similar to DNA ligase [Bacillus subtilis...	1574	9.60E-287
HGS018	gnl|PID|d1017321	DNA ligase [Synechocystis sp.] >pir|S744...	830	5.70E-209
HGS018	gi|1574651	DNA ligase (lig) [Haemophilus influenzae...	484	1.30E-204
HGS018	gi|607820	DNA ligase [Rhodothermus marinus] >sp|P4...	833	1.60E-204
HGS018	gi|155088	DNA ligase [Thermus aquaticus thermophil...	428	3.10E-201
HGS018	gi|609276	DNA ligase [Thermus scotoductus] >pir|S5...	436	1.10E-200
HGS018	gi|2983242	(AE000699) DNA ligase (NAD dependent) [A...	724	1.00E-179
HGS018	gi|49284	DNA ligase [Zymomonas mobilis] >pir|S206...	523	1.60E-170
HGS018	gnl|PID|e1237759	(AL021287) DNA ligase [Mycobacterium tub...	529	1.80E-161
HGS018	gnl|PID|e349403	DNA ligase [Mycobacterium leprae]	527	7.30E-160
HGS019	dbj||D86417_12	YflG [Bacillus subtilis] >gnl|PID|e11827...	559	8.00E-72
HGS019	gi|1044986	methionine aminopeptidase [Bacillus subt...	254	4.50E-58
HGS019	gi|1574578	methionine aminopeptidase (map) [Haemoph...	185	5.10E-56
HGS019	gnl|PID|e1172953	(AL008883) methionine aminopeptidase [My...	214	1.10E-51
HGS019	gi|2982825	(AE000672) methionyl aminopeptidase [Aqu...	192	3.70E-48
HGS019	gnl|PID|e1253272	(AL021958) methionine aminopeptidase [My...	130	5.20E-48
HGS019	gi|2687996	(AE001123) methionine aminopeptidase (ma...	195	9.00E-48
HGS019	gnl|PID|e1254451	methionine aminopeptidase [Streptomyces ...	151	2.10E-43

HGS019	gil975723	methionine aminopeptidase I [Saccharomyc...	294	3.60E-43
HGS019	gil2583129	(AC002387) putative methionine aminopept...	211	2.10E-41
HGS022	gnllPIDle1182648	alternate gene name: yedB; similar to am...	1586	2.80E-212
HGS022	gil2589195	(AF008553) Glu-tRNAGln amidotransferase ...	1436	1.70E-198
HGS022	gnllPIDld1018331	amidase [Synechocystis sp.] >pirlS77264l...	867	2.30E-178
HGS022	gil2982954	(AE000680) glutamyl-tRNA (Gln) amidotran...	1247	6.50E-176
HGS022	gil1224069	amidase [Moraxella catarrhalis] >splQ490...	522	4.40E-158
HGS022	gil2648182	(AE000943) Glu-tRNA amidotransferase, su...	548	1.30E-145
HGS022	gnllPIDle349405	probable amidase [Mycobacterium leprae]	465	6.30E-143
HGS022	gnllPIDle1237756	(AL021287) putative Glu-tRNA-Gln amidotr...	470	1.90E-141
HGS022	gil2313964	(AE000594) amidase [Helicobacter pylori]...	550	7.30E-123
HGS022	gil2622613	(AE000910) amidase [Methanobacterium the...	524	5.80E-116
HGS023	gil1354211	PET112-like protein [Bacillus subtilis] ...	2291	2.90E-307
HGS023	gil2653657	Bacillus subtilis PET112-like protein [B...	1313	1.20E-250
HGS023	gil2589196	(AF008553) Glu-tRNAGln amidotransferase ...	1315	4.20E-250
HGS023	gnllPIDle1182649	similar to pet112-like protein [Bacillus...	1346	7.10E-224
HGS023	gil2983123	(AE000691) glutamyl-tRNA (Gln) amidotran...	931	2.30E-165
HGS023	gnllPIDld1019042	PET112 [Synechocystis sp.] >pirlS75850lS...	859	4.10E-161
HGS023	gil1224071	unknown [Moraxella catarrhalis] >splQ490...	323	3.90E-132
HGS023	gil2313783	(AE000579) PET112-like protein [Helicoba...	664	6.80E-132
HGS023	gil2688237	(AE001140) glu-tRNA amidotransferase, su...	318	4.00E-131
HGS023	gil1590917	Glu-tRNA amidotransferase (gatB) [Methan...	263	8.60E-125
HGS024	gil2465557	(AF011545) YedA [Bacillus subtilis] >gil...	237	6.30E-27
HGS024	gnllPIDld1011444	hypothetical protein [Synechocystis sp.]...	153	8.60E-22
HGS024	gil2648183	(AE000943) Glu-tRNA amidotransferase, su...	126	1.80E-21
HGS024	gnllPIDle1237757	(AL021287) putative Glu-tRNA-Gln amidotr...	166	1.80E-17
HGS024	gil2984354	(AE000775) glutamyl-tRNA (Gln) amidotran...	102	2.70E-17
HGS024	gnllPIDle349616	hypothetical protein MLCB637.12 [Mycobac...	154	7.10E-16
HGS025	gnllPIDld1005830	stage V sporulation [Bacillus subtilis] ...	496	4.90E-69
HGS025	gnllPIDld1011124	peptidyl-tRNA hydrolase [Synechocystis s...	307	2.10E-49
HGS025	gil2983032	(AE000685) peptidyl-tRNA hydrolase [Aqui...	386	2.20E-49
HGS025	gnllPIDle304565	Pth [Mycobacterium tuberculosis] >gnllPI...	266	2.60E-43

HGS025	gil1045760	peptidyl-tRNA hydrolase homolog [Mycopla...	211	1.40E-39
HGS025	gil2314676	(AE000648) peptidyl-tRNA hydrolase (pth)...	102	3.30E-39
HGS025	gil1674312	(AE000058) Mycoplasma pneumoniae, peptid...	208	9.50E-39
HGS025	gil1127571	peptidyl-tRNA hydrolase [Chlamydia trach...	187	7.00E-37
HGS025	gil1573366	peptidyl-tRNA hydrolase (pth) [Haemophil...	201	8.50E-34
HGS025	gil581202	peptidyl-tRNA hydrolase [Escherichia col...	186	2.50E-27
HGS026	gil853776	peptide chain release factor 1 [Bacillus...	889	6.10E-160
HGS026	gnllPIDld1009421	Peptide Termination Factor [Mycoplasma c...	715	1.10E-126
HGS026	gnllPIDld1019559	peptide chain release factor [Synechocys...	539	2.70E-121
HGS026	gil2688096	(AE001130) peptide chain release factor ...	627	1.80E-115
HGS026	gnllPIDld1015453	Peptide chain release factor 1 (RF-1) [E...	467	3.90E-113
HGS026	gil968930	peptide chain release factor 1 [Escheric...	463	1.30E-112
HGS026	gil147567	peptide chain release factor 1 [Escheric...	467	3.40E-112
HGS026	gil154104	release factor 1 [Salmonella typhimurium...	460	2.90E-111
HGS026	gil1574404	polypeptide chain release factor 1 (prfA...	449	1.50E-109
HGS026	gil2313158	(AE000529) peptide chain release factor ...	576	1.20E-104
HGS028	gil2331287	(AF013188) release factor 2 [Bacillus...	769	2.50E-173
HGS028	splP28367lRF2_BACSU	PEPTIDE CHAIN RELEASE FACTOR 2 (RF-2)...	742	3.00E-157
HGS028	gil2984119	(AE000758) peptide chain release fact...	442	2.20E-128
HGS028	gnllPIDle254636	peptide release factor 2 [Bacillus fi...	718	2.90E-125
HGS028	pirlS76448lS76448	translation releasing factor RF-2 - S...	883	3.30E-116
HGS028	pirlA64190lA64190	translation releasing factor RF-2 - H...	444	1.70E-110
HGS028	gil154276	peptide chain release factor 2 [Salmo...	444	1.80E-108
HGS028	gil2687953	(AE001120) peptide chain release fact...	408	3.90E-108
HGS028	gil2367172	(AE000372) peptide chain release fact...	437	1.60E-107
HGS028	gil147569	peptide chain release factor 2 [Esche...	434	4.00E-107
HGS030	gnllPIDld1005806	unknown [Bacillus subtilis] >gnllPIDle11...	283	2.60E-64
HGS030	gil3176887	(AF065312) thymidylate kinase [Yersinia ...	124	3.00E-43
HGS030	gil2983484	(AE000716) thymidylate kinase [Aquifex a...	272	2.40E-37
HGS030	gil1244710	thymidylate kinase [Escherichia coli] >g...	136	7.20E-34
HGS030	gil2650584	(AE001102) thymidylate kinase (tmk) [Arc...	71	2.60E-30
HGS030	gil1045674	thymidylate kinase [Mycoplasma genitaliu...	173	8.20E-28

HGS030	gil1673808	(AE000016) Mycoplasma pneumoniae, thymid...	171	1.70E-27
HGS030	gil1246364	thymidylate:zeocin resistance protein:ND...	136	2.20E-27
HGS030	gil1246361	thymidine:thymidylate kinase:zeocin resi...	136	4.30E-27
HGS030	gil950071	ATP-bind. pyrimidine kinase [Mycoplasma ...	80	8.70E-21
HGS031	gnllPIDle1185242	uridylate kinase [Bacillus subtilis] >pi...	920	8.40E-123
HGS031	gnllPIDld1019291	uridine monophosphate kinase [Synechocys...	530	1.70E-96
HGS031	gnllPIDle1296663	(AL023797) uridylate kinase [Streptomyce...	678	2.10E-89
HGS031	gnllPIDle248883	hypothetical protein MTCY274.14c [Mycoba...	416	6.00E-89
HGS031	gnllPIDle327783	uridylate kinase [Mycobacterium leprae]	403	7.90E-86
HGS031	gil473234	uridine 5'-monophosphate (UMP) kinase [E...	384	2.10E-72
HGS031	gil1552748	uridine 5'-monophosphate (UMP) kinase [E...	375	3.60E-71
HGS031	gil1574616	mukB suppressor protein (smbA) [Haemophi...	409	3.70E-71
HGS031	gil2983290	(AE000703) UMP kinase [Aquifex aeolicus]	452	3.70E-58
HGS031	gil1518662	UMP kinase [Chlamydia trachomatis] >splP...	323	9.10E-55
HGS032	gil755152	highly hydrophobic integral membrane pro...	297	2.40E-81
HGS032	gil1235660	RfbA [Myxococcus xanthus] >splQ50862lRFB...	173	4.90E-24
HGS032	gnllPIDld1017629	ABC transporter [Synechocystis sp.] >pir...	149	1.50E-19
HGS032	gnllPIDld1029275	(AB010294) integral membrane component o...	126	6.40E-19
HGS032	gnllPIDld1008332	putative integral membrane component of ...	125	9.10E-19
HGS032	gnllPIDld1029271	(AB010293) integral membrane component o...	125	9.10E-19
HGS032	gnllPIDld1029279	(AB010295) integral membrane component o...	125	9.10E-19
HGS032	gnllPIDld1029264	(AB010150) integral membrane component o...	109	3.00E-15
HGS032	gil2983575	(AE000723) ABC transporter (ABC-2 subfam...	71	9.60E-13
HGS032	gil609595	homologous to kpsM (E.coli), bexB (H.inf...	78	2.60E-12
HGS033	gil755153	ATP-binding protein [Bacillus subtilis] ...	655	9.30E-94
HGS033	gil609596	ATP-binding protein [Serratia marcescens]	387	3.70E-69
HGS033	gil765059	ABC-transporter protein [Klebsiella pneu...	371	3.70E-69
HGS033	gil567183	ATP-binding protein [Klebsiella pneumoni...	367	1.20E-67
HGS033	gil304013	abcA [Aeromonas salmonicida] >pirlA36918...	294	7.20E-59
HGS033	gnllPIDld1020415	(AB002668) ABC transport protein [Actino...	323	4.00E-57
HGS033	gil1123030	CpxA [Actinobacillus pleuropneumoniae]	190	2.40E-56
HGS033	gil3135679	(AF064070) putative ABC-2 transporter hy...	219	2.10E-53

HGS033	gil2983576	(AE000723) ABC transporter [Aquifex aeol...	294	2.10E-53
HGS033	gil1235661	RfbB [Myxococcus xanthus] >splQ50863lRFB...	336	6.70E-53
HGS034	gil143467	ribosomal protein S4 [Bacillus subtilis]...	798	4.50E-106
HGS034	gil2314460	(AE000633) ribosomal protein S4 (rps4) [...	322	1.50E-62
HGS034	gil2982819	(AE000672) ribosomal protein S04 [Aquife...	253	2.00E-62
HGS034	gil606231	30S ribosomal subunit protein S4 [Escher...	292	2.40E-58
HGS034	gnllPIDle1234848	(AJ223236) ribosomal protein S4 [Salmone...	292	6.10E-58
HGS034	gil1573812	ribosomal protein S4 (rpS4) [Haemophilus...	292	1.60E-57
HGS034	gil639791	ribosomal protein S4 [Mycoplasma pneumon...	260	1.90E-56
HGS034	gil1046011	ribosomal protein S4 [Mycoplasma genital...	245	2.10E-54
HGS034	gnllPIDle316061	RpsD [Mycobacterium tuberculosis] >gnllP...	270	1.40E-52
HGS034	gil144143	ribosomal protein S4 [Buchnera aphidicol...	255	2.00E-51
HGS036	gil2648781	(AE000980) dipeptide ABC transporter, AT...	136	1.90E-40
HGS036	gnllPIDle1264523	(AL022121) putative peptide ABC transpor...	185	5.50E-35
HGS036	gil143607	sporulation protein [Bacillus subtilis]	191	7.70E-34
HGS036	gnllPIDle1183166	oligopeptide ABC transporter (ATP-bindin...	191	7.70E-34
HGS036	gnllPIDle1253461	oligopeptide transport ATP-binding prote...	213	5.50E-33
HGS036	gil2313342	(AE000544) oligopeptide ABC transporter,...	258	7.60E-32
HGS036	gnllPIDld1015858	Dipeptide transport ATP-binding protein ...	205	1.10E-31
HGS036	gil47346	AmiE protein [Streptococcus pneumoniae] ...	202	7.40E-31
HGS036	gil972897	DppD [Haemophilus influenzae] >gil157411...	204	1.40E-30
HGS036	gil677943	AppD [Bacillus subtilis] >gnllPIDle11831...	205	9.70E-30
HGS040	gnllPIDle1185713	elongation factor P [Bacillus subtilis] ...	702	7.00E-91
HGS040	gil1399829	elongation factor P [Synechococcus PCC79...	541	4.90E-69
HGS040	gnllPIDld1010902	elongation factor P [Synechocystis sp.] ...	535	3.20E-68
HGS040	gil951349	ORF1; putative [Anabaena sp.] >splQ44247...	505	3.80E-64
HGS040	gnllPIDle290977	unknown [Mycobacterium tuberculosis] >gn...	480	9.20E-61
HGS040	gnllPIDle1169516	elongation factor P [Corynebacterium glu...	460	4.80E-58
HGS040	gil2983772	(AE000736) elongation factor P [Aquifex ...	435	1.10E-54
HGS040	gil1658506	elongation factor P homologue; EF-P [Bac...	203	7.20E-52
HGS040	gil2313266	(AE000538) translation elongation factor...	409	4.00E-51
HGS040	gil536991	elongation factor P [Escherichia coli] >...	362	9.40E-45

168153_3	gnllPIDld1028815	(AB009524) Vi polysaccharide biosynthes...	237	5.80E-72
168153_3	gil47961	wcdB; ORF3 in citation [1] [Salmonella ...	234	1.80E-71
168153_3	gil1590951	UDP-glucose 4-epimerase (galE) [Methano...	148	3.20E-60
168153_3	pirlC69149lC69149	conserved hypothetical protein MTH380 -...	151	1.90E-50
168153_3	gil1143204	ORF2; Method: conceptual translation s...	227	4.50E-47
168153_3	gnllPIDle316552	unknown [Mycobacterium tuberculosis] >g...	109	4.70E-45
168153_3	gnllPIDle1185960	similar to NDP-sugar epimerase [Bacillu...	155	1.80E-39
168153_3	gnllPIDle1289548	(AL023093) putative sugar dehyratase [M...	86	1.80E-36
168153_3	gnllPIDle288124	glucose epimerase [Bacillus thuringiensis]	95	2.70E-35
168153_3	gil1591707	capsular polysaccharide biosynthesis pr...	85	1.60E-34
168153_2	gnllPIDle1184467	alternate gene name: yvhA [Bacillus subt...	354	4.90E-45
168153_2	gil1657652	Cap8M [Staphylococcus aureus]	138	9.00E-42
168153_2	gil1773352	Cap5M [Staphylococcus aureus]	138	9.00E-42
168153_2	gnllPIDle238668	hypothetical protein [Bacillus subtilis]...	139	6.10E-39
168153_2	gil1199573	spsB [Sphingomonas sp.] >gil1314578 gluc...	168	4.40E-35
168153_2	gnllPIDld1005318	ORF14 [Klebsiella pneumoniae] >splQ48460...	260	5.50E-33
168153_2	gnllPIDld1020425	(AB002668) galactosyltransferase [Actino...	155	5.60E-33
168153_2	gnllPIDld1029082	(AB010415) glycosyltransferase [Actinoba...	155	2.00E-32
168153_2	gnllPIDld1019174	galactosyl-1-phosphate transferase [Syne...	139	2.30E-32
168153_2	gnllPIDle220381	structural gene [Agrobacterium radiobacter]	138	2.40E-32
168153_1	gil1276880	EpsG [Streptococcus thermophilus]	141	3.40E-34
168153_1	gil1276879	EpsF [Streptococcus thermophilus]	162	1.70E-29
168153_1	gil633699	WbcQ [Yersinia enterocolitica] >pirlS512...	134	9.10E-26
168153_1	gnllPIDle238704	hypothetical protein [Bacillus subtilis]...	131	1.90E-18
168153_1	gil2983976	(AE000749) capsular polysaccharide biosy...	134	1.50E-15
168153_1	gnllPIDld1005311	ORF7 [Klebsiella pneumoniae] >splQ48453l...	94	2.10E-12
168153_1	gil633696	WbcN [Yersinia enterocolitica] >pirlS512...	123	2.50E-12
168153_1	gil755606	unknown [Bacillus subtilis]	144	5.40E-12
168153_1	gil1146237	21.4% of identity to trans-acting transc...	144	6.00E-12
168153_1	gnllPIDle238664	hypothetical protein [Bacillus subtilis]...	141	3.20E-11
168339_2	gnllPIDle1169894	putative repeating unit transporter ...	234	5.70E-57
168339_2	gil2209215	(AF004325) putative oligosaccharide ...	139	4.90E-37
168339_2	gil633692	Wzx [Yersinia enterocolitica] >pirlS...	141	3.00E-31
168339_2	gil2621404	(AE000819) O-antigen transporter [Me...	129	8.90E-29

168339_2	gi|2072448	EpsK [Lactococcus lactis cremoris]	199	4.00E-27
168339_2	sp|P37746|RFBX_ECOLI	PUTATIVE O-ANTIGEN TRANSPORTER.	140	2.10E-23
168339_2	gnl|PID|d1016603	Putative O-antigen transporter. [Esc...	140	2.90E-23
168339_2	gi|510252	membrane protein [Escherichia coli]	140	8.10E-23
168339_2	gi|2621427	(AE000822) O-antigen transporter [Me...	122	3.10E-20
168339_2	gi|152778	RFBX [Shigella dysenteriae] >pir|S34...	114	8.50E-19

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only nucleotides outside the 5' and 3' nucleotides of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 nucleotide subject sequence is aligned to a 100 nucleotide query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 nucleotides at 5' end. The 10 unpaired nucleotides represent 10% of the sequence (number of nucleotides at the 5' and 3' ends not matched/total number of nucleotides in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 nucleotides were perfectly matched the final percent identity would be 90%. In another example, a 90 nucleotide subject sequence is compared with a 100 nucleotide query sequence. This time the deletions are internal deletions so that there are no nucleotides on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only nucleotides 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of the present invention.

Vectors and Host Cell

The present invention also relates to vectors which include the isolated DNA molecules of the present invention, host cells comprising the recombinant vectors, and the production of *S. aureus* polypeptides and peptides of the present invention expressed by the host cells.

Recombinant constructs may be introduced into host cells using well known techniques such as infection, transduction, transfection, transvection, electroporation and transformation.. The vector may be, for example, a phage, plasmid, viral or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for

propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

Preferred are vectors comprising *cis*-acting control regions to the polynucleotide of interest. Appropriate *trans*-acting factors may be supplied by the host, supplied by a complementing vector or supplied by the vector itself upon introduction into the host.

In certain preferred embodiments in this regard, the vectors provide for specific expression, which may be inducible and/or cell type-specific. Particularly preferred among such vectors are those inducible by environmental factors that are easy to manipulate, such as temperature and nutrient additives.

Expression vectors useful in the present invention include chromosomal-, episomal- and virus-derived vectors, *e.g.*, vectors derived from bacterial plasmids, bacteriophage, yeast episomes, yeast chromosomal elements, viruses such as baculoviruses, papova viruses, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses and retroviruses, and vectors derived from combinations thereof, such as cosmids and phagemids.

The DNA insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli lac, trp* and *tac* promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination and, in the transcribed region, a ribosome binding site for translation. The coding portion of the mature transcripts expressed by the constructs will preferably include a translation initiating site at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin, or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE9, pQE10 available from Qiagen; pBS vectors, Phagescript vectors, Bluescript vectors, pNH8A, pNH16a, pNH18A, pNH46A available from Stratagene; pET series of vectors available from Novagen; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Among known bacterial promoters suitable for use in the present invention include the *E. coli lac*I and *lac*Z promoters, the T3, T5 and T7 promoters, the *gpt* promoter, the lambda PR and PL promoters and the *trp* promoter. Suitable eukaryotic promoters include the CMV immediate early promoter, the HSV thymidine kinase promoter, the early and late SV40 promoters, the promoters of retroviral LTRs, such as those of the Rous sarcoma virus (RSV), and metallothionein promoters, such as the mouse metallothionein-I promoter.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection or other methods. Such methods are described in many standard laboratory manuals (for example, Davis, *et al., Basic Methods In Molecular Biology* (1986)).

Transcription of DNA encoding the polypeptides of the present invention by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are *cis*-acting elements of DNA, usually about from 10 to 300 nucleotides that act to increase transcriptional activity of a promoter in a given host cell-type. Examples of enhancers include the SV40 enhancer, which is located on the late side of the replication origin at nucleotides 100 to 270, the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers.

For secretion of the translated polypeptide into the lumen of the endoplasmic reticulum, into the periplasmic space or into the extracellular environment, appropriate secretion signals may be incorporated into the expressed polypeptide, for example, the amino acid sequence KDEL. The signals may be endogenous to the polypeptide or they may be heterologous signals.

The polypeptide may be expressed in a modified form, such as a fusion protein, and may include not only secretion signals, but also additional heterologous functional regions. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to polypeptides to engender secretion or excretion, to improve stability and to facilitate purification, among others, are familiar and routine techniques in the art. A preferred fusion protein comprises a heterologous region from immunoglobulin that is useful to solubilize proteins. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is thoroughly advantageous for use in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262). On the other hand, for some uses it would be desirable to be able to delete the Fc part after the fusion protein has been expressed, detected and purified in the

advantageous manner described. This is the case when Fc portion proves to be a hindrance to use in therapy and diagnosis, for example when the fusion protein is to be used as antigen for immunizations. In drug discovery, for example, human proteins, such as, hIL5-receptor has been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See Bennett, D. et al. (1995) J. Molec. Recogn. 8:52-58 and Johanson, K. et al. (1995) J. Biol. Chem. 270 (16):9459-9471.

The *S. aureus* polypeptides can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography, lectin chromatography and high performance liquid chromatography ("HPLC") is employed for purification. Polypeptides of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect and mammalian cells.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses host cells that have been engineered to delete or replace endogenous genetic material (e.g. coding sequences for the polypeptides of the present invention), and/or to include genetic material (e.g. heterologous polynucleotide sequences) that is operably associated with polynucleotides of the present invention, and which activates, alters, and/or amplifies endogenous polynucleotides of the present invention. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g. promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g. U.S. Patent No. 5,641,670, issued June 24, 1997; Internation Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra, et al., Nature 342:435-438 (1989), the disclosures of each of which are hereby incorporated by reference in their entireties).

Polypeptides and Fragments

The invention further provides an isolated *S. aureus* polypeptide having an amino acid sequence in Table 1, or a peptide or polypeptide comprising a portion of the above polypeptides.

Variant and Mutant Polypeptides

To improve or alter the characteristics of *S. aureus* polypeptides of the present invention, protein engineering may be employed. Recombinant DNA technology known to those skilled in the art can be used to create novel mutant proteins or muteins including single or multiple amino acid substitutions, deletions, additions, or fusion proteins. Such modified

polypeptides can show, e.g., increased/decreased activity or increased/decreased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions. Further, the polypeptides of the present invention may be produced as multimers including dimers, trimers and tetramers. Multimerization may be facilitated by linkers or recombinantly though heterologous polypeptides such as Fc regions.

N-Terminal and C-Terminal Deletion Mutants

It is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function. For instance, Ron et al. J. Biol. Chem., 268:2984-2988 (1993), reported modified KGF proteins that had heparin binding activity even if 3, 8, or 27 N-terminal amino acid residues were missing. Accordingly, the present invention provides polypeptides having one or more residues deleted from the amino terminus of the polypeptides shown in Table 1.

Similarly, many examples of biologically functional C-terminal deletion mutants are known. For instance, Interferon gamma shows up to ten times higher activities by deleting 8-10 amino acid residues from the carboxy terminus of the protein *See, e.g.,* Dobeli, et al. (1988) J. Biotechnology 7:199-216. Accordingly, the present invention provides polypeptides having one or more residues from the carboxy terminus of the polypeptides shown in Table 1. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini as described below.

The present invention is further directed to polynucleotide encoding portions or fragments of the amino acid sequences described herein as well as to portions or fragments of the isolated amino acid sequences described herein. Fragments include portions of the amino acid sequences of Table 1, at least 7 contiguous amino acid in length, selected from any two integers, one of which representing a N-terminal position. The first codon of the polypeptides of Table 1 is position 1. Every combination of a N-terminal and C-terminal position that a fragment at least 7 contiguous amino acid residues in length could occupy, on any given amino acid sequence of Table 1 is included in the invention. At least means a fragment may be 7 contiguous amino acid residues in length or any integer between 7 and the number of residues in a full length amino acid sequence minus 1. Therefore, included in the invention are contiguous fragments specified by any N-terminal and C-terminal positions of amino acid sequence set forth in Table 1 wherein the contiguous fragment is any integer between 7 and the number of residues in a full length sequence minus 1.

Further, the invention includes polypeptides comprising fragments specified by size, in amino acid residues, rather than by N-terminal and C-terminal positions. The invention includes any fragment size, in contiguous amino acid residues, selected from integers between 7 and the number of residues in a full length sequence minus 1. Preferred sizes of contiguous polypeptide fragments include about 7 amino acid residues, about 10 amino acid residues,

about 20 amino acid residues, about 30 amino acid residues, about 40 amino acid residues, about 50 amino acid residues, about 100 amino acid residues, about 200 amino acid residues, about 300 amino acid residues, and about 400 amino acid residues. The preferred sizes are, of course, meant to exemplify, not limit, the present invention as all size fragments representing any integer between 7 and the number of residues in a full length sequence minus 1 are included in the invention. The present invention also provides for the exclusion of any fragments specified by N-terminal and C-terminal positions or by size in amino acid residues as described above. Any number of fragments specified by N-terminal and C-terminal positions or by size in amino acid residues as described above may be excluded.

The polypeptide fragments of the present invention can be immediately envisaged using the above description and are therefore not individually listed solely for the purpose of not unnecessarily lengthening the specification.

The above fragments need not be active since they would be useful, for example, in immunoassays, in epitope mapping, epitope tagging, to generate antibodies to a particular portion of the polypeptide, as vaccines, and as molecular weight markers.

Other Mutants

In addition to N- and C-terminal deletion forms of the protein discussed above, it also will be recognized by one of ordinary skill in the art that some amino acid sequences of the *S. aureus* polypeptides of the present invention can be varied without significant effect of the structure or function of the protein. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the protein which determine activity.

Thus, the invention further includes variations of the *S. aureus* polypeptides which show substantial *S. aureus* polypeptide activity or which include regions of *S. aureus* protein such as the protein portions discussed below. Such mutants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as to have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided. There are two main approaches for studying the tolerance of an amino acid sequence to change. *See*, Bowie, J. U. *et al.* (1990), Science 247:1306-1310. The first method relies on the process of evolution, in which mutations are either accepted or rejected by natural selection. The second approach uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene and selections or screens to identify sequences that maintain functionality.

These studies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The studies indicate which amino acid changes are likely to be permissive at a certain position of the protein. For example, most buried amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Other such phenotypically silent substitutions are described by Bowie et al. (*supra*) and the references cited therein. Typically seen as conservative substitutions are the replacements, one for another,

among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the aromatic residues Phe, Tyr.

Thus, the fragment, derivative, analog, or homolog of the polypeptide of Table 1 may be, for example: (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code: or (ii) one in which one or more of the amino acid residues includes a substituent group: or (iii) one in which the *S. aureus* polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol): or (iv) one in which the additional amino acids are fused to the above form of the polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the above form of the polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

Thus, the *S. aureus* polypeptides of the present invention may include one or more amino acid substitutions, deletions, or additions, either from natural mutations or human manipulation. As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein (see Table 3).

TABLE 3. Conservative Amino Acid Substitutions.

Aromatic	Phenylalanine Tryptophan Tyrosine
Hydrophobic	Leucine Isoleucine Valine
Polar	Glutamine Asparagine
Basic	Arginine Lysine Histidine
Acidic	Aspartic Acid Glutamic Acid
Small	Alanine Serine Threonine Methionine Glycine

Amino acids in the *S. aureus* proteins of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis. *See, e.g.*, Cunningham et al. (1989) Science 244:1081-1085. The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity using assays appropriate for measuring the function of the particular protein.

Of special interest are substitutions of charged amino acids with other charged or neutral amino acids which may produce proteins with highly desirable improved characteristics, such as less aggregation. Aggregation may not only reduce activity but also be problematic when preparing pharmaceutical formulations, because aggregates can be immunogenic. *See, e.g.*, Pinckard et al., (1967) Clin. Exp. Immunol. 2:331-340; Robbins, et al., (1987) Diabetes 36:838-845; Cleland, et al., (1993) Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377.

The polypeptides of the present invention are preferably provided in an isolated form, and may partially or substantially purified. A recombinantly produced version of the *S. aureus* polypeptide can be substantially purified by the one-step method described by Smith et al. (1988) Gene 67:31-40. Polypeptides of the invention also can be purified from natural or recombinant sources using antibodies directed against the polypeptides of the invention in methods which are well known in the art of protein purification. The purity of the polypeptide of the present invention may also specified in percent purity as relative to heterologous containing polypeptides. Preferred purities include at least 25%, 50%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.75%, and 100% pure, as relative to heretologous containing polypeptides.

The invention provides for isolated *S. aureus* polypeptides comprising an the amino acid sequence of a full-length *S. aureus* polypeptide having the complete amino acid sequence shown in Table 1 and the amino acid sequence of a full-length *S. aureus* polypeptide having the complete amino acid sequence shown in Table 1 excepting the N-terminal methionine The polypeptides of the present invention also include polypeptides having an amino acid sequence at least 80% identical, more preferably at least 90% identical, and still more preferably 95%, 96%, 97%, 98% or 99% identical to those described in (a), (b), (c), and (d) above. Further polypeptides of the present invention include polypeptides which have at least 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above.

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of a *S. aureus* polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 50 conservative amino acid substitutions, not more than 40 conservative amino acid substitutions, not more than 30 conservative amino acid substitutions, and not more than 20 conservative amino acid

substitutions. Also provided are polypeptides which comprise the amino acid sequence of a *S. aureus* polypeptide, having at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 conservative amino acid substitutions.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% (5 of 100) of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al., (1990) Comp. App. Biosci. 6:237-245. In a sequence alignment the query and subject sequences are both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, the results, in percent identity, must be manually corrected. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-

termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query amino acid residues outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not match/align with the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected. No other manual corrections are to made for the purposes of the present invention.

The above polypeptide sequences are included irrespective of whether they have their normal biological activity. This is because even where a particular polypeptide molecule does not have biological activity, one of skill in the art would still know how to use the polypeptide, for instance, as a vaccine or to generate antibodies. Other uses of the polypeptides of the present invention that do not have *S. aureus* activity include, *inter alia*, as epitope tags, in epitope mapping, and as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods known to those of skill in the art.

As described below, the polypeptides of the present invention can also be used to raise polyclonal and monoclonal antibodies, which are useful in assays for detecting *S. aureus* protein expression or as agonists and antagonists capable of enhancing or inhibiting *S. aureus* protein function. Further, such polypeptides can be used in the yeast two-hybrid system to "capture" *S. aureus* protein binding proteins which are also candidate agonists and antagonists according to the present invention. *See, e.g.,* Fields et al. (1989) Nature 340:245-246.

Epitope-Bearing Portions

In another aspect, the invention provides peptides and polypeptides comprising epitope-bearing portions of the polypeptides of the present invention. These epitopes are immunogenic or antigenic epitopes of the polypeptides of the present invention. An "immunogenic epitope" is defined as a part of a protein that elicits an antibody response when the whole protein or polypeptide is the immunogen. On the other hand, a region of a protein molecule to which an antibody can bind is defined as an "antigenic determinant" or "antigenic

epitope." The number of immunogenic epitopes of a protein generally is less than the number of antigenic epitopes. *See, e.g.*, Geysen, et al. (1983) Proc. Natl. Acad. Sci. USA 81:3998-4002. Predicted antigenic epitopes are shown in Table 4, below. It is pointed out that Table 4 only lists amino acid residues comprising epitopes predicted to have the highest degree of antigenicity by particular algorithm. The polypeptides not listed in Table 4 and portions of polypeptides not listed in Table 4 are not considered non-antigenic. This is because they may still be antigenic *in vivo* but merely not recognized as such by the particular algorithm used. Thus, Table 4 lists the amino acid residues comprising only preferred antigenic epitopes, not a complete list. In fact, all fragments of the polypeptide sequence of Table 1, at least 7 amino acids residues in length, are included in the present invention as being useful in epitope mapping and in making antibodies to particular portions of the polypeptides. Moreover, Table 4 lists only the critical residues of the epitopes determined by the Jameson-Wolf analysis. Thus, additional flanking residues on either the N-terminal, C-terminal, or both N- and C-terminal ends may be added to the sequences of Table 4 to generate a epitope-bearing portion at least 7 residues in length. Amino acid residues comprising other anigenic epitopes may be determined by algorithms similar to the Jameson-Wolf analysis or by *in vivo* testing for an antigenic response using the methods described herein or those known in the art.

TABLE 4. **Residues Comprising Antigenic Epitoes**

HGS001	from about Asp-47 to about Asp-50, from about Ser-128 to about Asp-130, from about Lys-265 to about Gly-267.
HGS005	from about Arg-104 to about Asp-106, from about Lys-116 to about Lys-120.
HGS007m	from about Glu-155 to about Gly-158, from about Gln-178 to about Gly-181, from about Ser-304 to about Cys-306, from about Asp-401 to about Tyr-403, from about Asn-405 to about Gly-408, from about Asp-411 to about Gly-416.
HGS009	from about Pro-257 to about Lys-259.
HGS014	from about Arg-186 to about Asp-188.
HGS019	from about Lys-98 to about Gly-100, from about Pro-187 to about Asp-189.
HGS023	from about Ser-251 to about Gly-253, from about Lys-437 to about Lys-440.
HGS025	from about Met-51 to about Gly-53.
HGS026	from about Asn-105 to about Lys-108, from about Glu-190 to about Gly-193, from about Arg-226 to about Ala-230.
HGS028	from about Ile-10 to about Tyr-13.
HGS030	from about Glu-11 to about Gly-14, from about Arg-147 to about Gln-149.
HGS033	from about Lys-143 to about Ser-145.
HGS034	from about Pro-33 to about Gln-35.
HGS036	from about Asp-64 to about Tyr-66, from about Asp-255 to about Tyr-257.
HGS040	from about Pro-30 to about Lys-32, from about Asp-76 to about Asp-78.
168153_3	from about Asn-35 to about Arg-37, from about Pro-135 to about Asp-138, from about Pro-185 to about Gln-188.
168153_2	from about Asp-54 to about Arg-56.
168153_1	from about Lys-64 to about Asp-67, from about Gln-319 to about Lys-322, from about Asn-342 to about Lys-344.
168339_2	from about Asn-82 to about Arg-85.

As to the selection of peptides or polypeptides bearing an antigenic epitope (*i.e.*, that contain a region of a protein molecule to which an antibody can bind), it is well known in that art that relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. *See, e.g.*, Sutcliffe, et al., (1983) Science 219:660-666. Peptides capable of eliciting protein-reactive sera are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins (*i.e.*, immunogenic epitopes) nor to the amino or carboxyl terminals. Peptides that are extremely hydrophobic and those of six or fewer residues generally are ineffective at inducing antibodies that bind to the mimicked protein; longer, peptides, especially those containing proline residues, usually are effective. *See,* Sutcliffe, et al., *supra*, p. 661. For instance, 18 of 20 peptides designed according to these guidelines, containing 8-39 residues covering 75% of the sequence of the influenza virus hemagglutinin HA1 polypeptide chain, induced antibodies that reacted with the HA1 protein or intact virus; and 12/12 peptides from the MuLV polymerase and 18/18 from the rabies glycoprotein induced antibodies that precipitated the respective proteins.

Antigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to raise antibodies, including monoclonal antibodies, that bind specifically to a polypeptide of the invention. Thus, a high proportion of hybridomas obtained by fusion of spleen cells from donors immunized with an antigen epitope-bearing peptide generally secrete antibody reactive with the native protein. *See* Sutcliffe, et al., *supra*, p. 663. The antibodies raised by antigenic epitope-bearing peptides or polypeptides are useful to detect the mimicked protein, and antibodies to different peptides may be used for tracking the fate of various regions of a protein precursor which undergoes post-translational processing. The peptides and anti-peptide antibodies may be used in a variety of qualitative or quantitative assays for the mimicked protein, for instance in competition assays since it has been shown that even short peptides (*e.g.*, about 9 amino acids) can bind and displace the larger peptides in immunoprecipitation assays. *See, e.g.,* Wilson, et al., (1984) Cell 37:767-778. The anti-peptide antibodies of the invention also are useful for purification of the mimicked protein, for instance, by adsorption chromatography using methods known in the art.

Antigenic epitope-bearing peptides and polypeptides of the invention designed according to the above guidelines preferably contain a sequence of at least seven, more preferably at least nine and most preferably between about 10 to about 50 amino acids (i.e. any integer between 7 and 50) contained within the amino acid sequence of a polypeptide of the invention. However, peptides or polypeptides comprising a larger portion of an amino acid sequence of a polypeptide of the invention, containing about 50 to about 100 amino acids, or any length up to and including the entire amino acid sequence of a polypeptide of the invention, also are considered epitope-bearing peptides or polypeptides of the invention and also are

useful for inducing antibodies that react with the mimicked protein. Preferably, the amino acid sequence of the epitope-bearing peptide is selected to provide substantial solubility in aqueous solvents (*i.e.*, the sequence includes relatively hydrophilic residues and highly hydrophobic sequences are preferably avoided); and sequences containing proline residues are particularly preferred.

Non-limiting examples of antigenic polypeptides or peptides that can be used to generate an Staphylococcal-specific immune response or antibodies include fragments of the amino acid sequences of Table 1 as discussed above. Table 4 discloses a list of non-limiting residues that are involved in the antigenicity of the epitope-bearing fragments of the present invention. Therefore, also included in the present inventions are isolated and purified antigenic epitope-bearing fragments of the polypeptides of the present invention comprising a peptide sequences of Table 4. The antigenic epitope-bearing fragments comprising a peptide sequence of Table 4 preferably contain between 7 to 50 amino acids (i.e. any integer between 7 and 50) of a polypeptide of the present invention. Also, included in the present invention are antigenic polypeptides between the integers of 7 and the full length sequence of a polypeptide of Table 1 comprising 1 or more amino acid sequences of Table 4. Therefore, in most cases, the polypeptides of Table 4 make up only a portion of the antigenic polypeptide. All combinations of sequences between the integers of 7 and the full sequence of a polypeptide sequence of Table 1 are included. The antigenic epitope-bearing fragments may be specified by either the number of contiguous amino acid residues or by specific N-terminal and C-terminal positions as described above for the polypeptide fragments of the present invention, wherein the first codon of each polypeptide sequence of Table 1 is position 1. Any number of the described antigenic epitope-bearing fragments of the present invention may also be excluded from the present invention in the same manner.

The epitope-bearing peptides and polypeptides of the invention may be produced by any conventional means for making peptides or polypeptides including recombinant means using nucleic acid molecules of the invention. For instance, an epitope-bearing amino acid sequence of the present invention may be fused to a larger polypeptide which acts as a carrier during recombinant production and purification, as well as during immunization to produce anti-peptide antibodies. Epitope-bearing peptides also may be synthesized using known methods of chemical synthesis. For instance, Houghten has described a simple method for synthesis of large numbers of peptides, such as 10-20 mg of 248 different 13 residue peptides representing single amino acid variants of a segment of the HA1 polypeptide which were prepared and characterized (by ELISA-type binding studies) in less than four weeks (Houghten, R. A. Proc. Natl. Acad. Sci. USA **82:**5131-5135 (1985)). This "Simultaneous Multiple Peptide Synthesis (SMPS)" process is further described in U.S. Patent No. 4,631,211 to Houghten and coworkers (1986). In this procedure the individual resins for the solid-phase synthesis of various peptides are contained in separate solvent-permeable packets, enabling the optimal use of the many identical repetitive steps involved in solid-phase methods.

A completely manual procedure allows 500-1000 or more syntheses to be conducted simultaneously (Houghten et al. (1985) Proc. Natl. Acad. Sci. 82:5131-5135 at 5134.

Epitope-bearing peptides and polypeptides of the invention are used to induce antibodies according to methods well known in the art. *See, e.g.,* Sutcliffe, et al., *supra*;; Wilson, et al., *supra*;; and Bittle, et al. (1985) J. Gen. Virol. 66:2347-2354. Generally, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling of the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine may be coupled to carrier using a linker such as m-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carrier using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier-coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 μg peptide or carrier protein and Freund's adjuvant. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

Immunogenic epitope-bearing peptides of the invention, *i.e.*, those parts of a protein that elicit an antibody response when the whole protein is the immunogen, are identified according to methods known in the art. For instance, Geysen, *et al.*, *supra*, discloses a procedure for rapid concurrent synthesis on solid supports of hundreds of peptides of sufficient purity to react in an ELISA. Interaction of synthesized peptides with antibodies is then easily detected without removing them from the support. In this manner a peptide bearing an immunogenic epitope of a desired protein may be identified routinely by one of ordinary skill in the art. For instance, the immunologically important epitope in the coat protein of foot-and-mouth disease virus was located by Geysen *et al. supra* with a resolution of seven amino acids by synthesis of an overlapping set of all 208 possible hexapeptides covering the entire 213 amino acid sequence of the protein. Then, a complete replacement set of peptides in which all 20 amino acids were substituted in turn at every position within the epitope were synthesized, and the particular amino acids conferring specificity for the reaction with antibody were determined. Thus, peptide analogs of the epitope-bearing peptides of the invention can be made routinely by this method. U.S. Patent No. 4,708,781 to Geysen (1987) further describes this method of identifying a peptide bearing an immunogenic epitope of a desired protein.

Further still, U.S. Patent No. 5,194,392, to Geysen (1990), describes a general method of detecting or determining the sequence of monomers (amino acids or other compounds) which is a topological equivalent of the epitope (*i.e.*, a "mimotope") which is

complementary to a particular paratope (antigen binding site) of an antibody of interest. More generally, U.S. Patent No. 4,433,092, also to Geysen (1989), describes a method of detecting or determining a sequence of monomers which is a topographical equivalent of a ligand which is complementary to the ligand binding site of a particular receptor of interest. Similarly, U.S. Patent No. 5,480,971 to Houghten, R. A. *et al.* (1996) discloses linear C_1-C_7-alkyl peralkylated oligopeptides and sets and libraries of such peptides, as well as methods for using such oligopeptide sets and libraries for determining the sequence of a peralkylated oligopeptide that preferentially binds to an acceptor molecule of interest. Thus, non-peptide analogs of the epitope-bearing peptides of the invention also can be made routinely by these methods. The entire disclosure of each document cited in this section on "Polypeptides and Fragments" is hereby incorporated herein by reference.

As one of skill in the art will appreciate, the polypeptides of the present invention and the epitope-bearing fragments thereof described above can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life *in vivo.* This has been shown, *e.g.*, for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EPA 0,394,827; Traunecker et al. (1988) Nature 331:84-86. Fusion proteins that have a disulfide-linked dimeric structure due to the IgG part can also be more efficient in binding and neutralizing other molecules than a monomeric *S. aureus* polypeptide or fragment thereof alone. *See* Fountoulakis et al. (1995) J. Biochem. 270:3958-3964. Nucleic acids encoding the above epitopes of *S. aureus* polypeptides can also be recombined with a gene of interest as an epitope tag to aid in detection and purification of the expressed polypeptide.

Antibodies

S. aureus polypeptide-specific antibodies for use in the present invention can be raised against the intact polypeptides of the present invention or an antigenic polypeptide fragment thereof, which may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough, without a carrier.

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules, single chain whole antibodies, and antibody fragments. Antibody fragments of the present invention include Fab and F(ab')2 and other fragments including single-chain Fvs (scFv) and disulfide-linked Fvs (sdFv). Also included in the present invention are chimeric and humanized monoclonal antibodies and polyclonal antibodies specific for the polypeptides of the present invention. The antibodies of the present invention may be prepared by any of a variety of methods. For example, cells expressing a polypeptide of the present invention or an antigenic fragment thereof can be administered to an animal in order to induce the production of sera containing polyclonal antibodies. For example, a preparation of a

polypeptide of the present invention or fragment thereof is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In a preferred method, the antibodies of the present invention are monoclonal antibodies or binding fragments thereof. Such monoclonal antibodies can be prepared using hybridoma technology. *See, e.g.,* Harlow et al., ANTIBODIES: A LABORATORY MANUAL, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: MONOCLONAL ANTIBODIES AND T-CELL HYBRIDOMAS 563-681 (Elsevier, N.Y., 1981). Fab and F(ab')2 fragments may be produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). Alternatively, *S. aureus* polypeptide-binding fragments, chimeric, and humanized antibodies can be produced through the application of recombinant DNA technology or through synthetic chemistry using methods known in the art.

Alternatively, additional antibodies capable of binding to the polypeptide antigen of the present invention may be produced in a two-step procedure through the use of anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and that, therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, *S. aureus* polypeptide-specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the *S. aureus* polypeptide-specific antibody can be blocked by the *S. aureus* polypeptide antigen. Such antibodies comprise anti-idiotypic antibodies to the *S. aureus* polypeptide-specific antibody and can be used to immunize an animal to induce formation of further *S. aureus* polypeptide-specific antibodies.

Antibodies and fragments thereof of the present invention may be described by the portion of a polypeptide of the present invention recognized or specifically bound by the antibody. Antibody binding fragments of a polypeptide of the present invention may be described or specified in the same manner as for polypeptide fragments discussed above., i.e, by N-terminal and C-terminal positions or by size in contiguous amino acid residues. Any number of antibody binding fragments, of a polypeptide of the present invention, specified by N-terminal and C-terminal positions or by size in amino acid residues, as described above, may also be excluded from the present invention. Therefore, the present invention includes antibodies that specifically bind a particularly described fragment of a polypeptide of the present invention and allows for the exclusion of the same.

Antibodies and fragments thereof of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies and fragments that do not bind polypeptides of any other species of *Staphylococcus* other than *S. aureus* or that only bind a particular strain of *S. aureus* are included in the present invention. Likewise, antibodies and fragments that bind only species of *Staphylococcus*, i.e. antibodies and fragments that do not

bind bacteria from any genus other than *Staphylococcus*, are included in the present invention.

Antibodies and fragments thereof of the present invention may also be described or specified in terms of their binding affinity. Preferred binding affinities include 10^{-7}M, 10^{-8}M, 10^{-9}M, 10^{-10}M, 10^{-11}M, 10^{-12}M and 10^{-13}M.

Diagnostic Assays

The present invention further relates to methods for assaying staphylococcal infection in an animal by detecting the expression of genes encoding staphylococcal polypeptides of the present invention. The methods comprise analyzing tissue or body fluid from the animal for *Staphylococcus*-specific antibodies, nucleic acids, or proteins. Analysis of nucleic acid specific to *Staphylococcus* is assayed by PCR or hybridization techniques using nucleic acid sequences of the present invention as either hybridization probes or primers. *See, e.g.,* Sambrook et al. Molecular cloning: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 2nd ed., 1989, page 54 reference); Eremeeva et al. (1994) J. Clin. Microbiol. 32:803-810 (describing differentiation among spotted fever group *Rickettsiae* species by analysis of restriction fragment length polymorphism of PCR-amplified DNA) and Chen et al. 1994 J. Clin. Microbiol. 32:589-595 (detecting bacterial nucleic acids *via* PCR).

Where diagnosis of a disease state related to infection with *Staphylococcus* has already been made, the present invention is useful for monitoring progression or regression of the disease state by measuring the amount of *Staphylococcus* cells present in a patient or whereby patients exhibiting enhanced *Staphylococcus* gene expression will experience a worse clinical outcome relative to patients expressing these gene(s) at a lower level.

By "biological sample" is intended any biological sample obtained from an animal, cell line, tissue culture, or other source which contains *Staphylococcus* polypeptide, mRNA, or DNA. Biological samples include body fluids (such as saliva, blood, plasma, urine, mucus, synovial fluid, etc.) tissues (such as muscle, skin, and cartilage) and any other biological source suspected of containing *Staphylococcus* polypeptides or nucleic acids. Methods for obtaining biological samples such as tissue are well known in the art.

The present invention is useful for detecting diseases related to *Staphylococcus* infections in animals. Preferred animals include monkeys, apes, cats, dogs, birds, cows, pigs, mice, horses, rabbits and humans. Particularly preferred are humans.

Total RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski et al. (1987) Anal. Biochem. 162:156-159. mRNA encoding *Staphylococcus* polypeptides having sufficient homology to the nucleic acid sequences identified in Table 1 to allow for hybridization between complementary sequences are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain

reaction (RT-LCR).

Northern blot analysis can be performed as described in Harada et al. (1990) Cell 63:303-312. Briefly, total RNA is prepared from a biological sample as described above. For the Northern blot, the RNA is denatured in an appropriate buffer (such as glyoxal/dimethyl sulfoxide/sodium phosphate buffer), subjected to agarose gel electrophoresis, and transferred onto a nitrocellulose filter. After the RNAs have been linked to the filter by a UV linker, the filter is prehybridized in a solution containing formamide, SSC, Denhardt's solution, denatured salmon sperm, SDS, and sodium phosphate buffer. A *S. aureus* polynucleotide sequence shown in Table 1 labeled according to any appropriate method (such as the ^{32}P-multiprimed DNA labeling system (Amersham)) is used as probe. After hybridization overnight, the filter is washed and exposed to x-ray film. DNA for use as probe according to the present invention is described in the sections above and will preferably at least 15 nucleotides in length.

S1 mapping can be performed as described in Fujita et al. (1987) Cell 49:357-367. To prepare probe DNA for use in S1 mapping, the sense strand of an above-described *S. aureus* DNA sequence of the present invention is used as a template to synthesize labeled antisense DNA. The antisense DNA can then be digested using an appropriate restriction endonuclease to generate further DNA probes of a desired length. Such antisense probes are useful for visualizing protected bands corresponding to the target mRNA (*i.e.*, mRNA encoding polypeptides of the present invention).

Levels of mRNA encoding *Staphylococcus* polypeptides are assayed, for *e.g.*, using the RT-PCR method described in Makino et al. (1990) Technique 2:295-301. By this method, the radioactivities of the "amplicons" in the polyacrylamide gel bands are linearly related to the initial concentration of the target mRNA. Briefly, this method involves adding total RNA isolated from a biological sample in a reaction mixture containing a RT primer and appropriate buffer. After incubating for primer annealing, the mixture can be supplemented with a RT buffer, dNTPs, DTT, RNase inhibitor and reverse transcriptase. After incubation to achieve reverse transcription of the RNA, the RT products are then subject to PCR using labeled primers. Alternatively, rather than labeling the primers, a labeled dNTP can be included in the PCR reaction mixture. PCR amplification can be performed in a DNA thermal cycler according to conventional techniques. After a suitable number of rounds to achieve amplification, the PCR reaction mixture is electrophoresed on a polyacrylamide gel. After drying the gel, the radioactivity of the appropriate bands (corresponding to the mRNA encoding the *Staphylococcus* polypeptides of the present invention) are quantified using an imaging analyzer. RT and PCR reaction ingredients and conditions, reagent and gel concentrations, and labeling methods are well known in the art. Variations on the RT-PCR method will be apparent to the skilled artisan. Other PCR methods that can detect the nucleic acid of the present invention can be found in PCR PRIMER: A LABORATORY MANUAL (C.W. Dieffenbach et al. eds., Cold Spring Harbor Lab Press, 1995).

The polynucleotides of the present invention, including both DNA and RNA, may be

used to detect polynucleotides of the present invention or *Staphylococcus* species including *S. aureus* using bio chip technology. The present invention includes both high density chip arrays (>1000 oligonucleotides per cm^2) and low density chip arrays (<1000 oligonucleotides per cm^2). Bio chips comprising arrays of polynucleotides of the present invention may be used to detect *Staphylococcus* species, including *S. aureus*, in biological and environmental samples and to diagnose an animal, including humans, with an *S. aureus* or other *Staphylococcus* infection. The bio chips of the present invention may comprise polynucleotide sequences of other pathogens including bacteria, viral, parasitic, and fungal polynucleotide sequences, in addition to the polynucleotide sequences of the present invention, for use in rapid differential pathogenic detection and diagnosis. The bio chips can also be used to monitor an *S. aureus* or other *Staphylococcus* infections and to monitor the genetic changes (deletions, insertions, mismatches, etc.) in response to drug therapy in the clinic and drug development in the laboratory. The bio chip technology comprising arrays of polynucleotides of the present invention may also be used to simultaneously monitor the expression of a multiplicity of genes, including those of the present invention. The polynucleotides used to comprise a selected array may be specified in the same manner as for the fragments, i.e, by their 5' and 3' positions or length in contigious base pairs and include from. Methods and particular uses of the polynucleotides of the present invention to detect *Staphylococcus* species, including *S. aureus*, using bio chip technology include those known in the art and those of: U.S. Patent Nos. 5510270, 5545531, 5445934, 5677195, 5532128, 5556752, 5527681, 5451683, 5424186, 5607646, 5658732 and World Patent Nos. WO/9710365, WO/9511995, WO/9743447, WO/9535505, each incorporated herein in their entireties.

Biosensors using the polynucleotides of the present invention may also be used to detect, diagnose, and monitor *S. aureus* or other *Staphylococcus* species and infections thereof. Biosensors using the polynucleotides of the present invention may also be used to detect particular polynucleotides of the present invention. Biosensors using the polynucleotides of the present invention may also be used to monitor the genetic changes (deletions, insertions, mismatches, etc.) in response to drug therapy in the clinic and drug development in the laboratory. Methods and particular uses of the polynucleotides of the present invention to detect *Staphylococcus* species, including *S. aureus*, using biosenors include those known in the art and those of: U.S. Patent Nos 5721102, 5658732, 5631170, and World Patent Nos. WO97/35011, WO/9720203, each incorporated herein in their entireties.

Thus, the present invention includes both bio chips and biosensors comprising polynucleotides of the present invention and methods of their use.

Assaying *Staphylococcus* polypeptide levels in a biological sample can occur using any art-known method, such as antibody-based techniques. For example, *Staphylococcus* polypeptide expression in tissues can be studied with classical immunohistological methods. In these, the specific recognition is provided by the primary antibody (polyclonal or

monoclonal) but the secondary detection system can utilize fluorescent, enzyme, or other conjugated secondary antibodies. As a result, an immunohistological staining of tissue section for pathological examination is obtained. Tissues can also be extracted, *e.g.*, with urea and neutral detergent, for the liberation of *Staphylococcus* polypeptides for Western-blot or dot/slot assay. *See, e.g.*, Jalkanen, M. et al. (1985) J. Cell. Biol. 101:976-985; Jalkanen, M. et al. (1987) J. Cell . Biol. 105:3087-3096. In this technique, which is based on the use of cationic solid phases, quantitation of a *Staphylococcus* polypeptide can be accomplished using an isolated *Staphylococcus* polypeptide as a standard. This technique can also be applied to body fluids.

Other antibody-based methods useful for detecting *Staphylococcus* polypeptide gene expression include immunoassays, such as the ELISA and the radioimmunoassay (RIA). For example, a *Staphylococcus* polypeptide-specific monoclonal antibodies can be used both as an immunoabsorbent and as an enzyme-labeled probe to detect and quantify a *Staphylococcus* polypeptide. The amount of a *Staphylococcus* polypeptide present in the sample can be calculated by reference to the amount present in a standard preparation using a linear regression computer algorithm. Such an ELISA is described in Iacobelli et al. (1988) Breast Cancer Research and Treatment 11:19-30. In another ELISA assay, two distinct specific monoclonal antibodies can be used to detect *Staphylococcus* polypeptides in a body fluid. In this assay, one of the antibodies is used as the immunoabsorbent and the other as the enzyme-labeled probe.

The above techniques may be conducted essentially as a "one-step" or "two-step" assay. The "one-step" assay involves contacting the *Staphylococcus* polypeptide with immobilized antibody and, without washing, contacting the mixture with the labeled antibody. The "two-step" assay involves washing before contacting the mixture with the labeled antibody. Other conventional methods may also be employed as suitable. It is usually desirable to immobilize one component of the assay system on a support, thereby allowing other components of the system to be brought into contact with the component and readily removed from the sample. Variations of the above and other immunological methods included in the present invention can also be found in Harlow et al., ANTIBODIES: A LABORATORY MANUAL, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988).

Suitable enzyme labels include, for example, those from the oxidase group, which catalyze the production of hydrogen peroxide by reacting with substrate. Glucose oxidase is particularly preferred as it has good stability and its substrate (glucose) is readily available. Activity of an oxidase label may be assayed by measuring the concentration of hydrogen peroxide formed by the enzyme-labeled antibody/substrate reaction. Besides enzymes, other suitable labels include radioisotopes, such as iodine (^{125}I, ^{121}I), carbon (^{14}C), sulphur (^{35}S), tritium (^{3}H), indium (^{112}In), and technetium (^{99m}Tc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

Further suitable labels for the *Staphylococcus* polypeptide-specific antibodies of the

present invention are provided below. Examples of suitable enzyme labels include malate dehydrogenase, Staphylococcus nuclease, delta-5-steroid isomerase, yeast-alcohol dehydrogenase, alpha-glycerol phosphate dehydrogenase, triose phosphate isomerase, peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase, and acetylcholine esterase.

Examples of suitable radioisotopic labels include ^{3}H, ^{111}In, ^{125}I, ^{131}I, ^{32}P, ^{35}S, ^{14}C, ^{51}Cr, ^{57}To, ^{58}Co, ^{59}Fe, ^{75}Se, ^{152}Eu, ^{90}Y, ^{67}Cu, ^{217}Ci, ^{211}At, ^{212}Pb, ^{47}Sc, ^{109}Pd, etc. ^{111}In is a preferred isotope where *in vivo* imaging is used since its avoids the problem of dehalogenation of the ^{125}I or ^{131}I-labeled monoclonal antibody by the liver. In addition, this radionucleotide has a more favorable gamma emission energy for imaging. *See, e.g.,* Perkins et al. (1985) Eur. J. Nucl. Med. 10:296-301; Carasquillo et al. (1987) J. Nucl. Med. 28:281-287. For example, ^{111}In coupled to monoclonal antibodies with 1-(P-isothiocyanatobenzyl)-DPTA has shown little uptake in non-tumors tissues, particularly the liver, and therefore enhances specificity of tumor localization. See, Esteban et al. (1987) J. Nucl. Med. 28:861-870.

Examples of suitable non-radioactive isotopic labels include ^{157}Gd, ^{55}Mn, ^{162}Dy, ^{52}Tr, and ^{56}Fe.

Examples of suitable fluorescent labels include an ^{152}Eu label, a fluorescein label, an isothiocyanate label, a rhodamine label, a phycoerythrin label, a phycocyanin label, an allophycocyanin label, an o-phthaldehyde label, and a fluorescamine label.

Examples of suitable toxin labels include, *Pseudomonas* toxin, diphtheria toxin, ricin, and cholera toxin.

Examples of chemiluminescent labels include a luminal label, an isoluminal label, an aromatic acridinium ester label, an imidazole label, an acridinium salt label, an oxalate ester label, a luciferin label, a luciferase label, and an aequorin label.

Examples of nuclear magnetic resonance contrasting agents include heavy metal nuclei such as Gd, Mn, and iron.

Typical techniques for binding the above-described labels to antibodies are provided by Kennedy et al. (1976) Clin. Chim. Acta 70:1-31, and Schurs et al. (1977) Clin. Chim. Acta 81:1-40. Coupling techniques mentioned in the latter are the glutaraldehyde method, the periodate method, the dimaleimide method, the m-maleimidobenzyl-N-hydroxy-succinimide ester method, all of which methods are incorporated by reference herein.

In a related aspect, the invention includes a diagnostic kit for use in screening serum containing antibodies specific against *S. aureus* infection. Such a kit may include an isolated *S. aureus* antigen comprising an epitope which is specifically immunoreactive with at least one anti-*S. aureus* antibody. Such a kit also includes means for detecting the binding of said antibody to the antigen. In specific embodiments, the kit may include a recombinantly produced or chemically synthesized peptide or polypeptide antigen. The peptide or polypeptide antigen may be attached to a solid support.

In a more specific embodiment, the detecting means of the above-described kit includes a solid support to which said peptide or polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the *S. aureus* antigen can be detected by binding of the reporter labeled antibody to the anti-*S. aureus* polypeptide antibody.

In a related aspect, the invention includes a method of detecting *S. aureus* infection in a subject. This detection method includes reacting a body fluid, preferably serum, from the subject with an isolated *S. aureus* antigen, and examining the antigen for the presence of bound antibody. In a specific embodiment, the method includes a polypeptide antigen attached to a solid support, and serum is reacted with the support. Subsequently, the support is reacted with a reporter-labeled anti-human antibody. The support is then examined for the presence of reporter-labeled antibody.

The solid surface reagent employed in the above assays and kits is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plates or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein , typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

The polypeptides and antibodies of the present invention, including fragments thereof, may be used to detect Staphylococcus species including *S. aureus* using bio chip and biosensor technology. Bio chip and biosensors of the present invention may comprise the polypeptides of the present invention to detect antibodies, which specifically recognize Staphylococcus species, including *S. aureus*. Bio chip and biosensors of the present invention may also comprise antibodies which specifically recognize the polypeptides of the present invention to detect Staphylococcus species, including *S. aureus* or specific polypeptides of the present invention. Bio chips or biosensors comprising polypeptides or antibodies of the present invention may be used to detect Staphylococcus species, including *S. aureus*, in biological and environmental samples and to diagnose an animal, including humans, with an *S. aureus* or other Staphylococcus infection. Thus, the present invention includes both bio chips and biosensors comprising polypeptides or antibodies of the present invention and methods of their use.

The bio chips of the present invention may further comprise polypeptide sequences of other pathogens including bacteria, viral, parasitic, and fungal polypeptide sequences, in addition to the polypeptide sequences of the, present invention, for use in rapid diffenertial pathogenic detection and diagnosis. The bio chips of the present invention may further comprise antibodies or fragements thereof specific for other pathogens including bacteria, viral, parasitic, and fungal polypeptide sequences, in addition to the antibodies or fragements thereof of the present invention, for use in rapid diffenertial pathogenic detection and diagnosis. The

bio chips and biosensors of the present invention may also be used to monitor an *S. aureus* or other Staphylococcus infection and to monitor the genetic changes (amio acid deletions, insertions, substitutions, etc.) in response to drug therapy in the clinic and drug development in the laboratory. The bio chip and biosensors comprising polypeptides or antibodies of the present invention may also be used to simultaneously monitor the expression of a multiplicity of polypeptides, including those of the present invention. The polypeptides used to comprise a bio chip or biosensor of the present invention may be specified in the same manner as for the fragements, i.e, by their N-terminal and C-terminal positions or length in contigious amino acid residue. Methods and particular uses of the polypeptides and antibodies of the present invention to detect Staphylococcus species, including *S. aureus*, or specific polypeptides using bio chip and biosensor technology include those known in the art, those of the U.S. Patent Nos. and World Patent Nos. listed above for bio chips and biosensors using polynucleotides of the present invention, and those of: U.S. Patent Nos. 5658732, 5135852, 5567301, 5677196, 5690894 and World Patent Nos. WO9729366, WO9612957, each incorporated herein in their entireties.

Treatment

Agonists and Antagonists - Assays and Molecules

The invention also provides a method of screening compounds to identify those which enhance or block the biological activity of the *S. aureus* polypeptides of the present invention. The present invention further provides where the compounds kill or slow the growth of *S. aureus*. The ability of *S. aureus* antagonists, including *S. aureus* ligands, to prophylactically or therapeutically block antibiotic resistance may be easily tested by the skilled artisan. *See, e.g.,* Straden et al. (1997) J Bacteriol. 179(1):9-16.

An agonist is a compound which increases the natural biological function or which functions in a manner similar to the polypeptides of the present invention, while antagonists decrease or eliminate such functions. Potential antagonists include small organic molecules, peptides, polypeptides, and antibodies that bind to a polypeptide of the invention and thereby inhibit or extinguish its activity.

The antagonists may be employed for instance to inhibit peptidoglycan cross bridge formation. Antibodies against *S. aureus* may be employed to bind to and inhibit *S. aureus* activity to treat antibiotic resistance. Any of the above antagonists may be employed in a composition with a pharmaceutically acceptable carrier.

Vaccines

The present invention also provides vaccines comprising one or more polypeptides of the present invention. Heterogeneity in the composition of a vaccine may be provided by combining *S. aureus* polypeptides of the present invention. Multi-component vaccines of this type are desirable because they are likely to be more effective in eliciting protective immune

responses against multiple species and strains of the *Staphylococcus* genus than single polypeptide vaccines.

Multi-component vaccines are known in the art to elicit antibody production to numerous immunogenic components. *See, e.g.*, Decker et al. (1996) J. Infect. Dis. 174:S270-275. In addition, a hepatitis B, diphtheria, tetanus, pertussis tetravalent vaccine has recently been demonstrated to elicit protective levels of antibodies in human infants against all four pathogenic agents. *See, e.g.*, Aristegui, J. et al. (1997) Vaccine 15:7-9.

The present invention in addition to single-component vaccines includes multi-component vaccines. These vaccines comprise more than one polypeptide, immunogen or antigen. Thus, a multi-component vaccine would be a vaccine comprising more than one of the *S. aureus* polypeptides of the present invention.

Further within the scope of the invention are whole cell and whole viral vaccines. Such vaccines may be produced recombinantly and involve the expression of one or more of the *S. aureus* polypeptides described in Table 1. For example, the *S. aureus* polypeptides of the present invention may be either secreted or localized intracellular, on the cell surface, or in the periplasmic space. Further, when a recombinant virus is used, the *S. aureus* polypeptides of the present invention may, for example, be localized in the viral envelope, on the surface of the capsid, or internally within the capsid. Whole cells vaccines which employ cells expressing heterologous proteins are known in the art. *See, e.g.*, Robinson, K. et al. (1997) Nature Biotech. 15:653-657; Sirard, J. et al. (1997) Infect. Immun. 65:2029-2033; Chabalgoity, J. et al. (1997) Infect. Immun. 65:2402-2412 . These cells may be administered live or may be killed prior to administration. Chabalgoity, J. et al., *supra*, for example, report the successful use in mice of a live attenuated *Salmonella* vaccine strain which expresses a portion of a platyhelminth fatty acid-binding protein as a fusion protein on its cells surface.

A multi-component vaccine can also be prepared using techniques known in the art by combining one or more *S. aureus* polypeptides of the present invention, or fragments thereof, with additional non-staphylococcal components (*e.g.*, diphtheria toxin or tetanus toxin, and/or other compounds known to elicit an immune response). Such vaccines are useful for eliciting protective immune responses to both members of the *Staphylococcus* genus and non-staphylococcal pathogenic agents.

The vaccines of the present invention also include DNA vaccines. DNA vaccines are currently being developed for a number of infectious diseases. *See, et al.*, Boyer, et al. (1997) Nat. Med. 3:526-532; reviewed in Spier, R. (1996) Vaccine 14:1285-1288. Such DNA vaccines contain a nucleotide sequence encoding one or more *S. aureus* polypeptides of the present invention oriented in a manner that allows for expression of the subject polypeptide. For example, the direct administration of plasmid DNA encoding *B. burgdorgeri* OspA has been shown to elicit protective immunity in mice against borrelial challenge. *See,* Luke et al. (1997) J. Infect. Dis. 175:91-97.

The present invention also relates to the administration of a vaccine which is

co-administered with a molecule capable of modulating immune responses. Kim et al. (1997) Nature Biotech. 15:641-646, for example, report the enhancement of immune responses produced by DNA immunizations when DNA sequences encoding molecules which stimulate the immune response are co-administered. In a similar fashion, the vaccines of the present invention may be co-administered with either nucleic acids encoding immune modulators or the immune modulators themselves. These immune modulators include granulocyte macrophage colony stimulating factor (GM-CSF) and CD86.

The vaccines of the present invention may be used to confer resistance to staphylococcal infection by either passive or active immunization. When the vaccines of the present invention are used to confer resistance to staphylococcal infection through active immunization, a vaccine of the present invention is administered to an animal to elicit a protective immune response which either prevents or attenuates a staphylococcal infection. When the vaccines of the present invention are used to confer resistance to staphylococcal infection through passive immunization, the vaccine is provided to a host animal (*e.g.*, human, dog, or mouse), and the antisera elicited by this antisera is recovered and directly provided to a recipient suspected of having an infection caused by a member of the *Staphylococcus* genus.

The ability to label antibodies, or fragments of antibodies, with toxin molecules provides an additional method for treating staphylococcal infections when passive immunization is conducted. In this embodiment, antibodies, or fragments of antibodies, capable of recognizing the *S. aureus* polypeptides disclosed herein, or fragments thereof, as well as other *Staphylococcus* proteins, are labeled with toxin molecules prior to their administration to the patient. When such toxin derivatized antibodies bind to *Staphylococcus* cells, toxin moieties will be localized to these cells and will cause their death.

The present invention thus concerns and provides a means for preventing or attenuating a staphylococcal infection resulting from organisms which have antigens that are recognized and bound by antisera produced in response to the polypeptides of the present invention. As used herein, a vaccine is said to prevent or attenuate a disease if its administration to an animal results either in the total or partial attenuation (*i.e.*, suppression) of a symptom or condition of the disease, or in the total or partial immunity of the animal to the disease.

The administration of the vaccine (or the antisera which it elicits) may be for either a "prophylactic" or "therapeutic" purpose. When provided prophylactically, the compound(s) are provided in advance of any symptoms of staphylococcal infection. The prophylactic administration of the compound(s) serves to prevent or attenuate any subsequent infection. When provided therapeutically, the compound(s) is provided upon or after the detection of symptoms which indicate that an animal may be infected with a member of the *Staphylococcus* genus. The therapeutic administration of the compound(s) serves to attenuate any actual infection. Thus, the *S. aureus* polypeptides, and fragments thereof, of the present invention may be provided either prior to the onset of infection (so as to prevent or attenuate an anticipated infection) or after the initiation of an actual infection.

The polypeptides of the invention, whether encoding a portion of a native protein or a functional derivative thereof, may be administered in pure form or may be coupled to a macromolecular carrier. Example of such carriers are proteins and carbohydrates. Suitable proteins which may act as macromolecular carrier for enhancing the immunogenicity of the polypeptides of the present invention include keyhole limpet hemacyanin (KLH) tetanus toxoid, pertussis toxin, bovine serum albumin, and ovalbumin. Methods for coupling the polypeptides of the present invention to such macromolecular carriers are disclosed in Harlow et al., ANTIBODIES: A LABORATORY MANUAL, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988).

A composition is said to be "pharmacologically or physiologically acceptable" if its administration can be tolerated by a recipient animal and is otherwise suitable for administration to that animal. Such an agent is said to be administered in a "therapeutically effective amount" if the amount administered is physiologically significant. An agent is physiologically significant if its presence results in a detectable change in the physiology of a recipient patient.

While in all instances the vaccine of the present invention is administered as a pharmacologically acceptable compound, one skilled in the art would recognize that the composition of a pharmacologically acceptable compound varies with the animal to which it is administered. For example, a vaccine intended for human use will generally not be co-administered with Freund's adjuvant. Further, the level of purity of the *S. aureus* polypeptides of the present invention will normally be higher when administered to a human than when administered to a non-human animal.

As would be understood by one of ordinary skill in the art, when the vaccine of the present invention is provided to an animal, it may be in a composition which may contain salts, buffers, adjuvants, or other substances which are desirable for improving the efficacy of the composition. Adjuvants are substances that can be used to specifically augment a specific immune response. These substances generally perform two functions: (1) they protect the antigen(s) from being rapidly catabolized after administration and (2) they nonspecifically stimulate immune responses.

Normally, the adjuvant and the composition are mixed prior to presentation to the immune system, or presented separately, but into the same site of the animal being immunized. Adjuvants can be loosely divided into several groups based upon their composition. These groups include oil adjuvants (for example, Freund's complete and incomplete), mineral salts (for example, $AlK(SO_4)_2$, $AlNa(SO_4)_2$, $AlNH_4(SO_4)$, silica, kaolin, and carbon), polynucleotides (for example, poly IC and poly AU acids), and certain natural substances (for example, wax D from *Mycobacterium tuberculosis*, as well as substances found in *Corynebacterium parvum*, or *Bordetella pertussis*, and members of the genus *Brucella*. Other substances useful as adjuvants are the saponins such as, for example, Quil A. (Superfos A/S, Denmark). Preferred adjuvants for use in the present invention include aluminum salts, such as $AlK(SO_4)_2$, $AlNa(SO_4)_2$, and $AlNH_4(SO_4)$. Examples of materials suitable for use in

vaccine compositions are provided in REMINGTON'S PHARMACEUTICAL SCIENCES 1324-1341 (A. Osol, ed, Mack Publishing Co, Easton, PA, (1980) (incorporated herein by reference).

The therapeutic compositions of the present invention can be administered parenterally by injection, rapid infusion, nasopharyngeal absorption (intranasopharangeally), dermoabsorption, or orally. The compositions may alternatively be administered intramuscularly, or intravenously. Compositions for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Carriers or occlusive dressings can be used to increase skin permeability and enhance antigen absorption. Liquid dosage forms for oral administration may generally comprise a liposome solution containing the liquid dosage form. Suitable forms for suspending liposomes include emulsions, suspensions, solutions, syrups, and elixirs containing inert diluents commonly used in the art, such as purified water. Besides the inert diluents, such compositions can also include adjuvants, wetting agents, emulsifying and suspending agents, or sweetening, flavoring, or perfuming agents.

Therapeutic compositions of the present invention can also be administered in encapsulated form. For example, intranasal immunization using vaccines encapsulated in biodegradable microsphere composed of poly(DL-lactide-co-glycolide). *See*, Shahin, R. et al. (1995) Infect. Immun. 63:1195-1200. Similarly, orally administered encapsulated *Salmonella typhimurium* antigens can also be used. Allaoui-Attarki, K. et al. (1997) Infect. Immun. 65:853-857. Encapsulated vaccines of the present invention can be administered by a variety of routes including those involving contacting the vaccine with mucous membranes (*e.g.*, intranasally, intracolonicly, intraduodenally).

Many different techniques exist for the timing of the immunizations when a multiple administration regimen is utilized. It is possible to use the compositions of the invention more than once to increase the levels and diversities of expression of the immunoglobulin repertoire expressed by the immunized animal. Typically, if multiple immunizations are given, they will be given one to two months apart.

According to the present invention, an "effective amount" of a therapeutic composition is one which is sufficient to achieve a desired biological effect. Generally, the dosage needed to provide an effective amount of the composition will vary depending upon such factors as the animal's or human's age, condition, sex, and extent of disease, if any, and other variables which can be adjusted by one of ordinary skill in the art.

The antigenic preparations of the invention can be administered by either single or multiple dosages of an effective amount. Effective amounts of the compositions of the invention can vary from 0.01-1,000 μg/ml per dose, more preferably 0.1-500 μg/ml per dose, and most preferably 10-300 μg/ml per dose.

Examples

Example 1: Isolation of a Selected DNA Clone From the Deposited Sample

Three approaches can be used to isolate a *S. aureus* clone comprising a polynucleotide of the present invention from any *S. aureus* genomic DNA library. The *S. aureus* strain ISP3 has been deposited as a convienent source for obtaining a *S. aureus* strain although a wide varity of strains *S. aureus* strains can be used which are known in the art.

S. aureus genomic DNA is prepared using the following method. A 20ml overnight bacterial culture grown in a rich medium (e.g., Trypticase Soy Broth, Brain Heart Infusion broth or Super broth), pelleted, washed two times with TES (3OmM Tris-pH 8.0, 25mM EDTA, 50mM NaCl), and resuspended in 5ml high salt TES (2.5M NaCl). Lysostaphin is added to final concentration of approx 50ug/ml and the mixture is rotated slowly 1 hour at 37C to make protoplast cells. The solution is then placed in incubator (or place in a shaking water bath) and warmed to 55C. Five hundred micro liter of 20% sarcosyl in TES (final concentration 2%) is then added to lyse the cells. Next, guanidine HCl is added to a final concentration of 7M (3.69g in 5.5 ml). The mixture is swirled slowly at 55C for 60-90 min (solution should clear). A CsCl gradient is then set up in SW41 ultra clear tubes using 2.0ml 5.7M CsCl and overlaying with 2.85M CsCl. The gradient is carefully overlayed with the DNA-containing GuHCl solution. The gradient is spun at 30,000 rpm, 20C for 24 hr and the lower DNA band is collected. The volume is increased to 5 ml with TE buffer. The DNA is then treated with protease K (10 ug/ml) overnight at 37 C, and precipitated with ethanol. The precipitated DNA is resuspended in a desired buffer.

In the first method, a plasmid is directly isolated by screening a plasmid *S. aureus* genomic DNA library using a polynucleotide probe corresponding to a polynucleotide of the present invention. Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (*See, e.g.*, Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).) The library is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art. *See, e.g.*, Sambrook et al. MOLECULAR CLONING: A LABORATORY MANUAL (Cold Spring Harbor, N.Y. 2nd ed. 1989); Ausubel et al., CURRENT PROTOCALS IN MOLECULAR BIOLOGY (John Wiley and Sons, N.Y. 1989). The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening. *See, e.g.*, Sambrook et al. MOLECULAR CLONING: A LABORATORY MANUAL (Cold Spring Harbor, N.Y. 2nd ed. 1989); Ausubel et al.,

CURRENT PROTOCALS IN MOLECULAR BIOLOGY (John Wiley and Sons, N.Y. 1989) or other techniques known to those of skill in the art.

Alternatively, two primers of 15-25 nucleotides derived from the 5' and 3' ends of a polynucleotide of Table 1 are synthesized and used to amplify the desired DNA by PCR using a *S. aureus* genomic DNA prep (e.g., the deposited *S. aureus* ISP3) as a template. PCR is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 ug of the above DNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Finally, overlapping oligos of the DNA sequences of Table 1 can be synthesized and used to generate a nucleotide sequence of desired length using PCR methods known in the art.

Example 2(a): Expression and Purification staphylococcal polypeptides in E. coli

The bacterial expression vector pQE60 is used for bacterial expression in this example. (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311). pQE60 encodes ampicillin antibiotic resistance ("Ampr") and contains a bacterial origin of replication ("ori"), an IPTG inducible promoter, a ribosome binding site ("RBS"), six codons encoding histidine residues that allow affinity purification using nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin (QIAGEN, Inc., *supra*) and suitable single restriction enzyme cleavage sites. These elements are arranged such that an inserted DNA fragment encoding a polypeptide expresses that polypeptide with the six His residues (i.e., a "6 X His tag") covalently linked to the carboxyl terminus of that polypeptide.

The DNA sequence encoding the desired portion of a *S. aureus* protein of the present invention is amplified from *S.* aureus genomic DNA or from the deposited DNA clone using PCR oligonucleotide primers which anneal to the 5' and 3' sequences coding for the portion of the *S. aureus* polynucleotide. Additional nucleotides containing restriction sites to facilitate cloning in the pQE60 vector are added to the 5' and 3' sequences, respectively.

For cloning the mature protein, the 5' primer has a sequence containing an appropriate restriction site followed by nucleotides of the amino terminal coding sequence of the desired *S. aureus* polynucleotide sequence in Table 1. One of ordinary skill in the art would appreciate that the point in the protein coding sequence where the 5' and 3' primers begin may be varied to amplify a DNA segment encoding any desired portion of the complete protein shorter or longer than the mature form. The 3' primer has a sequence containing an appropriate

restriction site followed by nucleotides complementary to the 3' end of the desired coding sequence of Table 1, excluding a stop codon, with the coding sequence aligned with the restriction site so as to maintain its reading frame with that of the six His codons in the pQE60 vector.

The amplified *S. aureus* DNA fragment and the vector pQE60 are digested with restriction enzymes which recognize the sites in the primers and the digested DNAs are then ligated together. The *S. aureus* DNA is inserted into the restricted pQE60 vector in a manner which places the *S. aureus* protein coding region downstream from the IPTG-inducible promoter and in-frame with an initiating AUG and the six histidine codons.

The ligation mixture is transformed into competent *E. coli* cells using standard procedures such as those described by Sambrook et al., *supra*. *E. coli* strain M15/rep4, containing multiple copies of the plasmid pREP4, which expresses the lac repressor and confers kanamycin resistance ("Kanr"), is used in carrying out the illustrative example described herein. This strain, which is only one of many that are suitable for expressing a *S. aureus* polypeptide, is available commercially (QIAGEN, Inc., *supra*). Transformants are identified by their ability to grow on LB plates in the presence of ampicillin and kanamycin. Plasmid DNA is isolated from resistant colonies and the identity of the cloned DNA confirmed by restriction analysis, PCR and DNA sequencing.

Clones containing the desired constructs are grown overnight ("O/N") in liquid culture in LB media supplemented with both ampicillin (100 μg/ml) and kanamycin (25 μg/ml). The O/N culture is used to inoculate a large culture, at a dilution of approximately 1:25 to 1:250. The cells are grown to an optical density at 600 nm ("OD600") of between 0.4 and 0.6. Isopropyl-β-D-thiogalactopyranoside ("IPTG") is then added to a final concentration of 1 mM to induce transcription from the lac repressor sensitive promoter, by inactivating the lacI repressor. Cells subsequently are incubated further for 3 to 4 hours. Cells then are harvested by centrifugation.

The cells are then stirred for 3-4 hours at 4°C in 6M guanidine-HCl, pH 8. The cell debris is removed by centrifugation, and the supernatant containing the *S. aureus* polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist, 1995, QIAGEN, Inc., *supra*). Briefly the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the *S. aureus* polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions

are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins can be eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4° C or frozen at -80° C.

Alternatively, the polypeptides of the present invention can be produced by a non-denaturing method. In this method, after the cells are harvested by centrifugation, the cell pellet from each liter of culture is resuspended in 25 ml of Lysis Buffer A at 4°C (Lysis Buffer A = 50 mM Na-phosphate, 300 mM NaCl, 10 mM 2-mercaptoethanol, 10% Glycerol, pH 7.5 with 1 tablet of Complete EDTA-free protease inhibitor cocktail (Boehringer Mannheim #1873580) per 50 ml of buffer). Absorbance at 550 nm is approximately 10-20 O.D./ml. The suspension is then put through three freeze/thaw cycles from -70°C (using a ethanol-dry ice bath) up to room temperature. The cells are lysed via sonication in short 10 sec bursts over 3 minutes at approximately 80W while kept on ice. The sonicated sample is then centrifuged at 15,000 RPM for 30 minutes at 4°C. The supernatant is passed through a column containing 1.0 ml of CL-4B resin to pre-clear the sample of any proteins that may bind to agarose non-specifically, and the flow-through fraction is collected.

The pre-cleared flow-through is applied to a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (Quiagen, Inc., *supra*). Proteins with a 6 X His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure. Briefly, the supernatant is loaded onto the column in Lysis Buffer A at 4°C, the column is first washed with 10 volumes of Lysis Buffer A until the A280 of the eluate returns to the baseline. Then, the column is washed with 5 volumes of 40 mM Imidazole (92% Lysis Buffer A / 8% Buffer B) (Buffer B = 50 mM Na-Phosphate, 300 mM NaCl, 10% Glycerol, 10 mM 2-mercaptoethanol, 500 mM Imidazole, pH of the final buffer should be 7.5). The protein is eluted off of the column with a series of increasing Imidazole solutions made by adjusting the ratios of Lysis Buffer A to Buffer B. Three different concentrations are used: 3 volumes of 75 mM Imidazole, 3 volumes of 150 mM Imidazole, 5 volumes of 500 mM Imidazole. The fractions containing the purified protein are analyzed using 8 %, 10 % or 14% SDS-PAGE depending on the protein size. The purified protein is then dialyzed 2X against phosphate-buffered saline (PBS) in order to place it into an easily workable buffer. The purified protein is stored at 4° C or frozen at -80°

The following is another alternative method may be used to purify *S. aureus* expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells are harvested by continuous centrifugation at 15,000 rpm

(Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 x *g* for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 x *g* centrifugation for 15 min., the pellet is discarded and the *S. aureus* polypeptide-containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 x *g*) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded *S. aureus* polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 mm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the *S. aureus* polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the *S. aureus* polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant *S. aureus* polypeptide exhibits greater than 95% purity after the above refolding and purification steps. No major contaminant bands are observed from Commassie

blue stained 16% SDS-PAGE gel when 5 μg of purified protein is loaded. The purified protein is also tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 2(b): Expression and Purification staphylococcal polypeptides in E. coli

Alternatively, the vector pQE10 can be used to clone and express polypeptides of the present invention. The difference being such that an inserted DNA fragment encoding a polypeptide expresses that polypeptide with the six His residues (i.e., a "6 X His tag") covalently linked to the amino terminus of that polypeptide. The bacterial expression vector pQE10 (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311) is used in this example . The components of the pQE10 plasmid are arranged such that the inserted DNA sequence encoding a polypeptide of the present invention expresses the polypeptide with the six His residues (*i.e.*, a "6 X His tag")) covalently linked to the amino terminus.

The DNA sequences encoding the desired portions of a polypeptide of Table 1 are amplified using PCR oligonucleotide primers from either genomic *S. aureus* DNA or DNA from the plasmid clones listed in Table 1 clones of the present invention. The PCR primers anneal to the nucleotide sequences encoding the desired amino acid sequence of a polypeptide of the present invention. Additional nucleotides containing restriction sites to facilitate cloning in the pQE10 vector are added to the 5' and 3' primer sequences, respectively.

For cloning a polypeptide of the present invention, the 5' and 3' primers are selected to amplify their respective nucleotide coding sequences. One of ordinary skill in the art would appreciate that the point in the protein coding sequence where the 5' and 3' primers begins may be varied to amplify a DNA segment encoding any desired portion of a polypeptide of the present invention. The 5' primer is designed so the coding sequence of the 6 X His tag is aligned with the restriction site so as to maintain its reading frame with that of *S. aureus* polypeptide. The 3' is designed to include an stop codon. The amplified DNA fragment is then cloned, and the protein expressed, as described above for the pQE60 plasmid.

The DNA sequences encoding the amino acid sequences of Table 1 may also be cloned and expressed as fusion proteins by a protocol similar to that described directly above, wherein the pET-32b(+) vector (Novagen, 601 Science Drive, Madison, WI 53711) is preferentially used in place of pQE10.

Example 2(c): Expression and Purification of Stahphlococcusl polypeptides in E. coli

The bacterial expression vector pQE60 is used for bacterial expression in this example (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311). However, in this example, the polypeptide coding sequence is inserted such that translation of the six His codons is prevented

and, therefore, the polypeptide is produced with no 6 X His tag.

The DNA sequence encoding the desired portion of the *S. aureus* amino acid sequence is amplified from a *S. aureus* genomic DNA prep using PCR oligonucleotide primers which anneal to the 5' and 3' nucleotide sequences corresponding to the desired portion of the *S. aureus* polypeptides. Additional nucleotides containing restriction sites to facilitate cloning in the pQE60 vector are added to the 5' and 3' primer sequences.

For cloning a *S. aureus* polypeptides of the present invention, 5' and 3' primers are selected to amplify their respective nucleotide coding sequences. One of ordinary skill in the art would appreciate that the point in the protein coding sequence where the 5' and 3' primers begin may be varied to amplify a DNA segment encoding any desired portion of a polypeptide of the present invention. The 3' and 5' primers contain appropriate restriction sites followed by nucleotides complementary to the 5' and 3' ends of the coding sequence respectively. The 3' primer is additionally designed to include an in-frame stop codon.

The amplified *S. aureus* DNA fragments and the vector pQE60 are digested with restriction enzymes recognizing the sites in the primers and the digested DNAs are then ligated together. Insertion of the *S. aureus* DNA into the restricted pQE60 vector places the *S. aureus* protein coding region including its associated stop codon downstream from the IPTG-inducible promoter and in-frame with an initiating AUG. The associated stop codon prevents translation of the six histidine codons downstream of the insertion point.

The ligation mixture is transformed into competent *E. coli* cells using standard procedures such as those described by Sambrook et al. *E. coli* strain M15/rep4, containing multiple copies of the plasmid pREP4, which expresses the lac repressor and confers kanamycin resistance ("Kanr"), is used in carrying out the illustrative example described herein. This strain, which is only one of many that are suitable for expressing *S. aureus* polypeptide, is available commercially (QIAGEN, Inc., *supra*). Transformants are identified by their ability to grow on LB plates in the presence of ampicillin and kanamycin. Plasmid DNA is isolated from resistant colonies and the identity of the cloned DNA confirmed by restriction analysis, PCR and DNA sequencing.

Clones containing the desired constructs are grown overnight ("O/N") in liquid culture in LB media supplemented with both ampicillin (100 μg/ml) and kanamycin (25 μg/ml). The O/N culture is used to inoculate a large culture, at a dilution of approximately 1:25 to 1:250. The cells are grown to an optical density at 600 nm ("OD600") of between 0.4 and 0.6. isopropyl-b-D-thiogalactopyranoside ("IPTG") is then added to a final concentration of 1 mM to induce transcription from the *lac* repressor sensitive promoter, by inactivating the lacI repressor. Cells subsequently are incubated further for 3 to 4 hours. Cells then are harvested by centrifugation.

To purify the *S. aureus* polypeptide, the cells are then stirred for 3-4 hours at 4°C in 6M guanidine-HCl, pH 8. The cell debris is removed by centrifugation, and the supernatant

containing the *S. aureus* polypeptide is dialyzed against 50 mM Na-acetate buffer pH 6, supplemented with 200 mM NaCl. Alternatively, the protein can be successfully refolded by dialyzing it against 500 mM NaCl, 20% glycerol, 25 mM Tris/HCl pH 7.4, containing protease inhibitors. After renaturation the protein can be purified by ion exchange, hydrophobic interaction and size exclusion chromatography. Alternatively, an affinity chromatography step such as an antibody column can be used to obtain pure *S. aureus* polypeptide. The purified protein is stored at 4° C or frozen at -80° C.

The following alternative method may be used to purify *S. aureus* polypeptides expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells are harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells ware then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 x *g* for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 x *g* centrifugation for 15 min., the pellet is discarded and the *S. aureus* polypeptide-containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 x *g*) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded *S. aureus* polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 μm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 mm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-

PAGE.

Fractions containing the *S. aureus* polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the *S. aureus* polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant *S. aureus* polypeptide exhibits greater than 95% purity after the above refolding and purification steps. No major contaminant bands are observed from Commassie blue stained 16% SDS-PAGE gel when 5 μg of purified protein is loaded. The purified protein is also tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 2(d): Cloning and Expression of S. aureus in Other Bacteria

S. aureus polypeptides can also be produced in: *S. aureus* using the methods of S. Skinner et al., (1988) Mol. Microbiol. 2:289-297 or J. I. Moreno (1996) Protein Expr. Purif. 8(3):332-340; *Lactobacillus* using the methods of C. Rush et al., 1997 Appl. Microbiol. Biotechnol. 47(5):537-542; or in *Bacillus subtilis* using the methods Chang et al., U.S. Patent No. 4,952,508.

Example 3: Cloning and Expression in COS Cells

A *S. aureus* expression plasmid is made by cloning a portion of the DNA encoding a *S. aureus* polypeptide into the expression vector pDNAI/Amp or pDNAIII (which can be obtained from Invitrogen, Inc.). The expression vector pDNAI/amp contains: (1) an *E. coli* origin of replication effective for propagation in *E. coli* and other prokaryotic cells; (2) an ampicillin resistance gene for selection of plasmid-containing prokaryotic cells; (3) an SV40 origin of replication for propagation in eukaryotic cells; (4) a CMV promoter, a polylinker, an SV40 intron; (5) several codons encoding a hemagglutinin fragment (i.e., an "HA" tag to facilitate purification) followed by a termination codon and polyadenylation signal arranged so that a DNA can be conveniently placed under expression control of the CMV promoter and operably linked to the SV40 intron and the polyadenylation signal by means of restriction sites in the polylinker. The HA tag corresponds to an epitope derived from the influenza hemagglutinin protein described by Wilson et al. 1984 Cell 37:767. The fusion of the HA tag to the target protein allows easy detection and recovery of the recombinant protein with an

antibody that recognizes the HA epitope. pDNAIII contains, in addition, the selectable neomycin marker.

A DNA fragment encoding a *S. aureus* polypeptide is cloned into the polylinker region of the vector so that recombinant protein expression is directed by the CMV promoter. The plasmid construction strategy is as follows. The DNA from a *S. aureus* genomic DNA prep is amplified using primers that contain convenient restriction sites, much as described above for construction of vectors for expression of *S. aureus* in *E. coli*. The 5' primer contains a Kozak sequence, an AUG start codon, and nucleotides of the 5' coding region of the *S. aureus* polypeptide. The 3' primer, contains nucleotides complementary to the 3' coding sequence of the *S. aureus* DNA, a stop codon, and a convenient restriction site.

The PCR amplified DNA fragment and the vector, pDNAI/Amp, are digested with appropriate restriction enzymes and then ligated. The ligation mixture is transformed into an appropriate *E. coli* strain such as SURE™ (Stratagene Cloning Systems, La Jolla, CA 92037), and the transformed culture is plated on ampicillin media plates which then are incubated to allow growth of ampicillin resistant colonies. Plasmid DNA is isolated from resistant colonies and examined by restriction analysis or other means for the presence of the fragment encoding the *S. aureus* polypeptide

For expression of a recombinant *S. aureus* polypeptide, COS cells are transfected with an expression vector, as described above, using DEAE-dextran, as described, for instance, by Sambrook et al. (*supra*). Cells are incubated under conditions for expression of *S. aureus* by the vector.

Expression of the *S. aureus*-HA fusion protein is detected by radiolabeling and immunoprecipitation, using methods described in, for example Harlow et al., *supra*.. To this end, two days after transfection, the cells are labeled by incubation in media containing ^{35}S-cysteine for 8 hours. The cells and the media are collected, and the cells are washed and the lysed with detergent-containing RIPA buffer: 150 mM NaCl, 1% NP-40, 0.1% SDS, 1% NP-40, 0.5% DOC, 50 mM TRIS, pH 7.5, as described by Wilson et al. (*supra*). Proteins are precipitated from the cell lysate and from the culture media using an HA-specific monoclonal antibody. The precipitated proteins then are analyzed by SDS-PAGE and autoradiography. An expression product of the expected size is seen in the cell lysate, which is not seen in negative controls.

Example 4: Cloning and Expression in CHO Cells

The vector pC4 is used for the expression of *S. aureus* polypeptide in this example. Plasmid pC4 is a derivative of the plasmid pSV2-dhfr (ATCC Accession No. 37146). The plasmid contains the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary cells or other cells lacking dihydrofolate activity that are transfected with these plasmids can be selected by growing the cells in a selective medium (alpha minus MEM, Life

Technologies) supplemented with the chemotherapeutic agent methotrexate. The amplification of the DHFR genes in cells resistant to methotrexate (MTX) has been well documented. *See, e.g.*, Alt et al., 1978, J. Biol. Chem. 253:1357-1370; Hamlin et al., 1990, Biochem. et Biophys. Acta, 1097:107-143; Page et al., 1991, Biotechnology 9:64-68. Cells grown in increasing concentrations of MTX develop resistance to the drug by overproducing the target enzyme, DHFR, as a result of amplification of the DHFR gene. If a second gene is linked to the DHFR gene, it is usually co-amplified and over-expressed. It is known in the art that this approach may be used to develop cell lines carrying more than 1,000 copies of the amplified gene(s). Subsequently, when the methotrexate is withdrawn, cell lines are obtained which contain the amplified gene integrated into one or more chromosome(s) of the host cell.

Plasmid pC4 contains the strong promoter of the long terminal repeat (LTR) of the Rouse Sarcoma Virus, for expressing a polypeptide of interest, Cullen, et al. (1985) Mol. Cell. Biol. 5:438-447; plus a fragment isolated from the enhancer of the immediate early gene of human cytomegalovirus (CMV), Boshart, et al., 1985, Cell 41:521-530. Downstream of the promoter are the following single restriction enzyme cleavage sites that allow the integration of the genes: *Bam* HI, *Xba* I, and *Asp* 718. Behind these cloning sites the plasmid contains the 3' intron and polyadenylation site of the rat preproinsulin gene. Other high efficiency promoters can also be used for the expression, e.g., the human ß-actin promoter, the SV40 early or late promoters or the long terminal repeats from other retroviruses, e.g., HIV and HTLVI. Clontech's Tet-Off and Tet-On gene expression systems and similar systems can be used to express the *S. aureus* polypeptide in a regulated way in mammalian cells (Gossen et al., 1992, Proc. Natl. Acad. Sci. USA 89:5547-5551. For the polyadenylation of the mRNA other signals, e.g., from the human growth hormone or globin genes can be used as well. Stable cell lines carrying a gene of interest integrated into the chromosomes can also be selected upon co-transfection with a selectable marker such as gpt, G418 or hygromycin. It is advantageous to use more than one selectable marker in the beginning, e.g., G418 plus methotrexate.

The plasmid pC4 is digested with the restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel. The DNA sequence encoding the *S. aureus* polypeptide is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the desired portion of the gene. A 5' primer containing a restriction site, a Kozak sequence, an AUG start codon, and nucleotides of the 5' coding region of the *S. aureus* polypeptide is synthesized and used. A 3' primer, containing a restriction site, stop codon, and nucleotides complementary to the 3' coding sequence of the *S. aureus* polypeptides is synthesized and used. The amplified fragment is digested with the restriction endonucleases and then purified again on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC4 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene are used for transfection. Five μg of the expression plasmid pC4 is cotransfected with 0.5 μg of the plasmid pSVneo using a lipid-mediated transfection agent such as Lipofectin™ or LipofectAMINE.™ (LifeTechnologies Gaithersburg, MD). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μM, 2 μM, 5 μM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100-200 μM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 5: Quantitative Murine Soft Tissue Infection Model for S. aureus

Compositions of the present invention, including polypeptides and peptides, are assayed for their ability to function as vaccines or to enhance/stimulate an immune response to a bacterial species (e.g., *S. aureus*) using the following quantitative murine soft tissue infection model. Mice (e.g., NIH Swiss female mice, approximately 7 weeks old) are first treated with a biologically protective effective amount, or immune enhancing/stimulating effective amount of a composition of the present invention using methods known in the art, such as those discussed above. *See, e.g.*, Harlow et al., ANTIBODIES: A LABORATORY MANUAL, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988). An example of an appropriate starting dose is 20ug per animal.

The desired bacterial species used to challenge the mice, such as *S. aureus*, is grown as an overnight culture. The culture is diluted to a concentration of 5 X 10^8 cfu/ml, in an appropriate media, mixed well, serially diluted, and titered. The desired doses are further diluted 1:2 with sterilized Cytodex 3 microcarrier beads preswollen in sterile PBS (3g/100ml). Mice are anesthetize briefly until docile, but still mobile and injected with 0.2 ml of the Cytodex 3 bead/bacterial mixture into each animal subcutaneously in the inguinal region. After four days, counting the day of injection as day one, mice are sacrificed and the contents of the abscess is excised and placed in a 15 ml conical tube containing 1.0ml of sterile PBS. The contents of the abscess is then enzymatically treated and plated as follows.

The abscess is first disrupted by vortexing with sterilized glass beads placed in the tubes. 3.0mls of prepared enzyme mixture (1.0ml Collagenase D (4.0 mg/ml), 1.0ml Trypsin (6.0

mg/ml) and 8.0 ml PBS) is then added to each tube followed by a 20 min. incubation at 37C. The solution is then centrifuged and the supernatant drawn off. 0.5 ml dH20 is then added and the tubes are vortexed and then incubated for 10 min. at room temperature. 0.5 ml media is then added and samples are serially diluted and plated onto agar plates, and grown overnight at 37C. Plates with distinct and separate colonies are then counted, compared to positive and negative control samples, and quantified. The method can be used to identify composition and determine appropriate and effective doses for humans and other animals by comparing the effective doses of compositions of the present invention with compositions known in the art to be effective in both mice and humans. Doses for the effective treatment of humans and other animals, using compositions of the present invention, are extrapolated using the data from the above experiments of mice. It is appreciated that further studies in humans and other animals may be needed to determine the most effective doses using methods of clinical practice known in the art.

Example 6: Murine Systemic Neutropenic Model for S. aureus Infection

Compositions of the present invention, including polypeptides and peptides, are assayed for their ability to function as vaccines or to enhance/stimulate an immune response to a bacterial species (e.g., *S. aureus*) using the following qualitative murine systemic neutropenic model. Mice (e.g., NIH Swiss female mice, approximately 7 weeks old) are first treated with a biologically protective effective amount, or immune enhancing/stimulating effective amount of a composition of the present invention using methods known in the art, such as those discussed above. *See, e.g.,* Harlow et al., ANTIBODIES: A LABORATORY MANUAL, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988). An example of an appropriate starting dose is 20ug per animal.

Mice are then injected with 250 - 300 mg/kg cyclophosphamide intraperitonially. Counting the day of C.P. injection as day one, the mice are left untreated for 5 days to begin recovery of PMNL'S.

The desired bacterial species used to challenge the mice, such as *S. aureus*, is grown as an overnight culture. The culture is diluted to a concentration of 5 X 10^8 cfu/ml, in an appropriate media, mixed well, serially diluted, and titered. The desired doses are further diluted 1:2 in 4% Brewer's yeast in media.

Mice are injected with the bacteria/brewer's yeast challenge intraperitonially. The Brewer's yeast solution alone is used as a control. The mice are then monitored twice daily for the first week following challenge, and once a day for the next week to ascertain morbidity and mortality. Mice remaining at the end of the experiment are sacrificed. The method can be used to identify compositions and determine appropriate and effective doses for humans and other animals by comparing the effective doses of compositions of the present invention with compositions known in the art to be effective in both mice and humans. Doses for the effective treatment of humans and other animals, using compositions of the present invention, are

extrapolated using the data from the above experiments of mice. It is appreciated that further studies in humans and other animals may be needed to determine the most effective doses using methods of clinical practice known in the art.

The disclosure of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein and the sequence listings are hereby incorporated by reference in their entireties.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention. Functionally equivalent methods and components are within the scope of the invention, in addition to those shown and described herein and will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13*bis*)

A. The indications made below relate to the microorganism referred to in the description on page 9, line 18.

B. IDENTIFICATION OF DEPOSIT — Further deposits are identified on an additional sheet ☐

Name of depositary institution American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
7 April 1998	202108

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* — This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the International Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only	For International Bureau use only
☐ This sheet was received with the international application	☐ This sheet was received by the International Bureau on:
Authorized officer	Authorized officer

ATCC Deposit No. 202108

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 202108

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence selected from the group consisting of:

   (a) a nucleotide sequence encoding any one of the amino acid sequences of the polypeptides shown in Table 1;

   (b) a nucleotide sequence complementary to any one of the nucleotide sequences in (a)

   (c) a nucleotide sequence at least 95% identical to any one of the nucleotide sequences shown in Table 1; and

   (d) a nucleotide sequence at least 95% identical to a nucleotide sequence complementary to any one of the nucleotide sequences shown in Table 1.

2. An isolated nucleic acid molecule of claim 1 comprising a polynucleotide which hybridizes under stringent hybridization conditions to a polynucleotide having a nucleotide sequence identical to a nucleotide sequence in (a) or (b) of claim 1.

3. An isolated nucleic acid molecule of claim 1 comprising a polynucleotide which encodes an epitope-bearing portion of a polypeptide in (a) of claim 1.

4. The isolated nucleic acid molecule of claim 3, wherein said epitope-bearing portion of a polypeptide comprises an amino acid sequence listed in Table 4.

5. A method for making a recombinant vector comprising inserting an isolated nucleic acid molecule of claim 1 into a vector.

6. A recombinant vector produced by the method of claim 5.

7. A host cell comprising the vector of claim 6.

8. A method of producing a polypeptide comprising:

   (a) growing the host cell of claim 7 such that the protein is expressed by the cell; and

   (b) recovering the expressed polypeptide.

9. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

   (a) a complete amino acid sequences of Table 1;

   (b) a complete amino acid sequence of Table 1 except the N-terminal residue; and

   (c) a fragment of a polypeptide of Table 1 having biological activity; and

(d) a fragment of a polypeptide of Table 1 which binds to an antibody specific for a *S. aureus* polypeptide.

10. An isolated polypeptide comprising an amino acid sequence at least 95% identical to an amino acid sequence of Table 1.

11. An isolated epitope-bearing polypeptide comprising an amino acid sequence of Table 4.

12. An isolated antibody specific for the polypeptide of claim 9.

13. A host cell which produces an antibody of claim 12.

16. A vaccine, comprising:

(1) one or more *S. aureus* polypeptides selected from the group consisting of a polypeptide of claim 9; and

(2) a pharmaceutically acceptable diluent, carrier, or excipient;

wherein said polypeptide is present, in an amount effective to elicit protective antibodies in an animal to a member of the *Staphylococcus* genus.

17. A method of preventing or attenuating an infection caused by a member of the *Staphylococcus* genus in an animal, comprising administering to said animal a polypeptide of claim 9, wherein said polypeptide is administered in an amount effective to prevent or attenuate said infection.

18. A method of detecting *Staphylococcus* nucleic acids in a biological sample comprising:

(a) contacting the sample with one or more nucleic acids of claim 1, under conditions such that hybridization occurs; and

(b) detecting hybridization of said nucleic acids to the one or more *Staphylococcus* nucleic acid sequences present in the biological sample.

19. A method of detecting *Staphylococcus* antibodies in a biological sample obtained from an animal, comprising

(a) contacting the sample with a polypeptide of claim 9; and

(b) detecting antibody-antigen complexes.

20. A method of detecting a polypeptide of claim 9 comprising:

(a) obtaining a biological sample suspected of containing said polypeptide;

(c) contacting said sample with antibody which specifically binds said polypeptide; and

(c) determining the presence or absence of said polypeptide in said biological sample.

SEQUENCE LISTING

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Glu Arg Ile Asn Asp
420

<210> 9
<211> 1537
<212> DNA
<213> Staphylococcus aureus

<400> 9
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atgcctgaaa gagaacgtac atctcctcag tatgaatcat tccacgaatt gtacaagaac 180
tatactacca aggaactcac tcaaaaagct aaaactctta agttgacgaa ccatagtaaa 240
ttaaataaaa aagaacttgt tctagctatt atggaagcac aaatggaaaa agatggtaac 300
tattatatgg aaggtatctt agatgatata caaccaggtg gttatggttt tttaagaaca 360
gtgaactatt ctaaagggga aaaagatatt tatatatctg ctagccaaat tcgtcgtttt 420
gaaattaaac gtggggataa agtaactggg aaagttagaa aacctaaaga taacgaaaaa 480
tattatggct tattacaagt tgactttgtc aatgaccata acgcagaaga agtgaagaaa 540
cgtccgcatt tccaagcttt gacaccactt tatccagatg agcgtattaa attagagaca 600
gaaatacaaa attattcaac gcgcatcatg gatttagtaa caccgattgg tttaggtcaa 660
cgtggtttaa tagtggcgcc acctaaagca ggtaaaacat cgttattaaa agaaatagcg 720
aatgcaatca gtacgaacaa accagatgca aagctattta ttttgttagt tggcgagcgt 780
cctgaagagg taacagattt agaacgctca gtagaagctg ctgaagtcgt tcattcaacg 840
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cgcgcttata acttagttat tccaccaagt ggtcgtacat tatcaggtgg tttagatcct 1020
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agtttaacaa tacttgcaac tgcattagtt gatacgggtt cacgtatgga cgatatgatt 1140

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gactttactg aaagatttat tcgcaaactt aaaaggtcta agaataatga agatttcttc 1380
aagcagctac aaaagtctgc agaagaaagt actaaaacgg gtcgacctat aatttaataa 1440
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<210> 10
<211> 438
<212> PRT
<213> Staphylococcus aureus

<400> 10

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Leu Tyr Lys Asn Tyr Thr Thr Lys Glu Leu Thr Gln Lys Ala Lys Thr
            20                  25                  30

Leu Lys Leu Thr Asn His Ser Lys Leu Asn Lys Lys Glu Leu Val Leu
        35                  40                  45

Ala Ile Met Glu Ala Gln Met Glu Lys Asp Gly Asn Tyr Tyr Met Glu
    50                  55                  60

Gly Ile Leu Asp Asp Ile Gln Pro Gly Gly Tyr Gly Phe Leu Arg Thr
65                  70                  75                  80

Val Asn Tyr Ser Lys Gly Glu Lys Asp Ile Tyr Ile Ser Ala Ser Gln
                85                  90                  95

Ile Arg Arg Phe Glu Ile Lys Arg Gly Asp Lys Val Thr Gly Lys Val
            100                 105                 110

Arg Lys Pro Lys Asp Asn Glu Lys Tyr Tyr Gly Leu Leu Gln Val Asp
        115                 120                 125

Phe Val Asn Asp His Asn Ala Glu Glu Val Lys Lys Arg Pro His Phe
    130                 135                 140

Gln Ala Leu Thr Pro Leu Tyr Pro Asp Glu Arg Ile Lys Leu Glu Thr
145                 150                 155                 160

Glu Ile Gln Asn Tyr Ser Thr Arg Ile Met Asp Leu Val Thr Pro Ile
                165                 170                 175

Gly Leu Gly Gln Arg Gly Leu Ile Val Ala Pro Pro Lys Ala Gly Lys
            180                 185                 190

Thr Ser Leu Leu Lys Glu Ile Ala Asn Ala Ile Ser Thr Asn Lys Pro
        195                 200                 205

Asp Ala Lys Leu Phe Ile Leu Leu Val Gly Glu Arg Pro Glu Glu Val
    210                 215                 220

Thr Asp Leu Glu Arg Ser Val Glu Ala Ala Glu Val Val His Ser Thr
225                 230                 235                 240

Phe Asp Glu Pro Pro Glu His His Val Lys Val Ala Glu Leu Leu Leu
                245                 250                 255
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Glu Arg Ala Lys Arg Leu Val Glu Ile Gly Glu Asp Val Ile Ile Leu
260 265 270

Met Asp Ser Ile Thr Arg Leu Ala Arg Ala Tyr Asn Leu Val Ile Pro
275 280 285

Pro Ser Gly Arg Thr Leu Ser Gly Gly Leu Asp Pro Ala Ser Leu His
290 295 300

Lys Pro Lys Ala Phe Phe Gly Ala Ala Arg Asn Ile Glu Ala Gly Gly
305 310 315 320

Ser Leu Thr Ile Leu Ala Thr Ala Leu Val Asp Thr Gly Ser Arg Met
325 330 335

Asp Asp Met Ile Tyr Glu Glu Phe Lys Gly Thr Gly Asn Met Glu Leu
340 345 350

His Leu Asp Arg Lys Leu Ser Glu Arg Arg Ile Phe Pro Ala Ile Asp
355 360 365

Ile Gly Arg Ser Ser Thr Arg Lys Glu Glu Leu Leu Ile Ser Lys Ser
370 375 380

Glu Leu Asp Thr Leu Trp Gln Leu Arg Asn Leu Phe Thr Asp Ser Thr
385 390 395 400

Asp Phe Thr Glu Arg Phe Ile Arg Lys Leu Lys Arg Ser Lys Asn Asn
405 410 415

Glu Asp Phe Phe Lys Gln Leu Gln Lys Ser Ala Glu Glu Ser Thr Lys
420 425 430

Thr Gly Arg Pro Ile Ile
435

<210> 11
<211> 554
<212> DNA
<213> Staphylococcus aureus

<400> 11
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ccgaattaaa aagaatgcag attttcagag aatatataaa aaaggtcatt ctgtagccaa 180
cagacaattt gttgtataca cttgtaataa taaagaaata gaccattttc gcttaggtat 240
tagtgtttct aaaaaactag gtaatgcagt gttaagaaac aagattaaaa gagcaatacg 300
tgaaaatttc aaagtacata agtcgcatat attggccaaa gatattattg taatagcaag 360
acagccagct aaagatatga cgactttaca aatacagaat agtcttgagc acgtacttaa 420
aattgccaaa gtttttaata aaaagattaa gtaaggatag ggtaggggaa ggaaaacatt 480
aaccactcaa cacatcccga agtcttacct cagacaaacg taagactgac cttagggtta 540
taataactta cttt 554

<210> 12
<211> 117
<212> PRT
<213> Staphylococcus aureus

<400> 12

10

Met Leu Leu Glu Lys Ala Tyr Arg Ile Lys Lys Asn Ala Asp Phe Gln
1 5 10 15

Arg Ile Tyr Lys Lys Gly His Ser Val Ala Asn Arg Gln Phe Val Val
20 25 30

Tyr Thr Cys Asn Asn Lys Glu Ile Asp His Phe Arg Leu Gly Ile Ser
35 40 45

Val Ser Lys Lys Leu Gly Asn Ala Val Leu Arg Asn Lys Ile Lys Arg
50 55 60

Ala Ile Arg Glu Asn Phe Lys Val His Lys Ser His Ile Leu Ala Lys
65 70 75 80

Asp Ile Ile Val Ile Ala Arg Gln Pro Ala Lys Asp Met Thr Thr Leu
85 90 95

Gln Ile Gln Asn Ser Leu Glu His Val Leu Lys Ile Ala Lys Val Phe
100 105 110

Asn Lys Lys Ile Lys
115

<210> 13
<211> 1712
<212> DNA
<213> Staphylococcus aureus

<400> 13
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gaattcattc cctaggatat acgaatgtac ctgttaaatt agataaagaa gttgaaggta 180
caattcgcgt acacacagtt gaacaataaa gttggattga aataagaggt gtaaccattc 240
atggatagaa tgtatgagca aaatcaaatg ccgcataaca atgaagctga acagtctgtc 300
ttaggttcaa ttattataga tccagaattg attaatacta ctcaggaagt tttgcttcct 360
gagtcgtttt ataggggtgc ccatcaacat attttccgtg caatgatgca cttaaatgaa 420
gataataaag aaattgatgt tgtaacattg atggatcaat tatcgacgga aggtacgttg 480
aatgaagcgg gtggcccgca atatcttgca gagttatcta caaatgtacc aacgacgcga 540
aatgttcagt attatactga tatcgtttct aagcatgcat taaaacgtag attgattcaa 600
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<210> 14
<211> 466
<212> PRT
<213> Staphylococcus aureus

<400> 14
Met Asp Arg Met Tyr Glu Gln Asn Gln Met Pro His Asn Asn Glu Ala
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Glu Gln Ser Val Leu Gly Ser Ile Ile Ile Asp Pro Glu Leu Ile Asn
            20   25   30

Thr Thr Gln Glu Val Leu Leu Pro Glu Ser Phe Tyr Arg Gly Ala His
        35   40   45

Gln His Ile Phe Arg Ala Met Met His Leu Asn Glu Asp Asn Lys Glu
    50   55   60

Ile Asp Val Val Thr Leu Met Asp Gln Leu Ser Thr Glu Gly Thr Leu
65   70   75   80

Asn Glu Ala Gly Gly Pro Gln Tyr Leu Ala Glu Leu Ser Thr Asn Val
                85   90   95

Pro Thr Thr Arg Asn Val Gln Tyr Tyr Thr Asp Ile Val Ser Lys His
            100   105   110

Ala Leu Lys Arg Arg Leu Ile Gln Thr Ala Asp Ser Ile Ala Asn Asp
        115   120   125

Gly Tyr Asn Asp Glu Leu Glu Leu Asp Ala Ile Leu Ser Asp Ala Glu
    130   135   140

Arg Arg Ile Leu Glu Leu Ser Ser Ser Arg Glu Ser Asp Gly Phe Lys
145   150   155   160

Asp Ile Arg Asp Val Leu Gly Gln Val Tyr Glu Thr Ala Glu Glu Leu
                165   170   175

Asp Gln Asn Ser Gly Gln Thr Pro Gly Ile Pro Thr Gly Tyr Arg Asp
            180   185   190

Leu Asp Gln Met Thr Ala Gly Phe Asn Arg Asn Asp Leu Ile Ile Leu
        195   200   205

Ala Ala Arg Pro Ser Val Gly Lys Thr Ala Phe Ala Leu Asn Ile Ala
    210   215   220

Gln Lys Val Ala Thr His Glu Asp Met Tyr Thr Val Gly Ile Phe Ser
225   230   235   240

Leu Glu Met Gly Ala Asp Gln Leu Ala Thr Arg Met Ile Cys Ser Ser
                245   250   255

Gly Asn Val Asp Ser Asn Arg Leu Arg Thr Gly Thr Met Thr Glu Glu
            260   265   270

Asp Trp Ser Arg Phe Thr Ile Ala Val Gly Lys Leu Ser Arg Thr Lys
        275   280   285

Ile Phe Ile Asp Asp Thr Pro Gly Ile Arg Ile Asn Asp Leu Arg Ser

    290   295   300

Lys Cys Arg Arg Leu Lys Gln Glu His Gly Leu Asp Met Ile Val Ile
305   310   315   320

Asp Tyr Leu Gln Leu Ile Gln Gly Ser Gly Ser Arg Ala Ser Asp Asn
                325   330   335

Arg Gln Gln Glu Val Ser Glu Ile Ser Arg Thr Leu Lys Ala Leu Ala
            340   345   350

Arg Glu Leu Lys Cys Pro Val Ile Ala Leu Ser Gln Leu Ser Arg Gly
        355   360   365

Val Glu Gln Arg Gln Asp Lys Arg Pro Met Met Ser Asp Ile Arg Glu
    370   375   380

Ser Gly Ser Ile Glu Gln Asp Ala Asp Ile Val Ala Phe Leu Tyr Arg
385   390   395   400

Asp Asp Tyr Tyr Asn Arg Gly Gly Asp Glu Asp Asp Asp Asp Asp Gly
                405   410   415

Gly Phe Glu Pro Gln Thr Asn Asp Glu Asn Gly Glu Ile Glu Ile Ile
            420   425   430

Ile Ala Lys Gln Arg Asn Gly Pro Thr Gly Thr Val Lys Leu His Phe
        435   440   445

Met Lys Gln Tyr Asn Lys Phe Thr Asp Ile Asp Tyr Ala His Ala Asp
    450   455   460

Met Met
465

<210> 15
<211> 1170
<212> DNA
<213> Staphylococcus aureus

<400> 15
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aaacaatgaa agagactgta ggtgaatcaa atgagtaaaa cagcaattat ttttccggga 180
caaggtgccc aaaaagttgg tatggcgcaa gatttgttta acaacaatga tcaagcaact 240
gaaattttaa cttcagcagc gaacacatta gactttgata ttttagagac aatgtttact 300
gatgaagaag gtaaattggg tgaaactgaa aacacacaac cagctttatt gacgcatagt 360
tcggcattat tagcagcgct aaaaaatttg aatcctgatt ttactatggg gcatagttta 420
ggtgaatatt caagtttagt tgcagctgac gtattatcat ttgaagatgc agttaaaatt 480
gttagaaaac gtggtcaatt aatggcgcaa gcatttccta ctggtgtagg aagcatggct 540
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gacaaaataa ttgaaccagc aaacattaat tgcccaggtc aaattgttgt ttcaggtcac 660
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tcaagttaca ttaatcaatt tgaatggcgt gatgctaagt ttcctgtagt tcaaaatgta 840
aatgcgcaag gtgaaactga caaagaagta attaaatcta atatggtcaa gcaattatat 900
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tgctttagta acaggtgcat caagaggaat tggacgtagt attgcgttac aattagcaga 1140

agaaggatat aatgtagcag taaactatgc 1170

<210> 16
<211> 308
<212> PRT
<213> Staphylococcus aureus

<400> 16
Met Ser Lys Thr Ala Ile Ile Phe Pro Gly Gln Gly Ala Gln Lys Val
1 5 10 15

Gly Met Ala Gln Asp Leu Phe Asn Asn Asn Asp Gln Ala Thr Glu Ile
20 25 30

Leu Thr Ser Ala Ala Asn Thr Leu Asp Phe Asp Ile Leu Glu Thr Met
35 40 45

Phe Thr Asp Glu Glu Gly Lys Leu Gly Glu Thr Glu Asn Thr Gln Pro
50 55 60

Ala Leu Leu Thr His Ser Ser Ala Leu Leu Ala Ala Leu Lys Asn Leu
65 70 75 80

Asn Pro Asp Phe Thr Met Gly His Ser Leu Gly Glu Tyr Ser Ser Leu
85 90 95

Val Ala Ala Asp Val Leu Ser Phe Glu Asp Ala Val Lys Ile Val Arg
100 105 110

Lys Arg Gly Gln Leu Met Ala Gln Ala Phe Pro Thr Gly Val Gly Ser
115 120 125

Met Ala Ala Val Leu Gly Leu Asp Phe Asp Lys Val Asp Glu Ile Cys
130 135 140

Lys Ser Leu Ser Ser Asp Asp Lys Ile Ile Glu Pro Ala Asn Ile Asn
145 150 155 160

Cys Pro Gly Gln Ile Val Val Ser Gly His Lys Ala Leu Ile Asp Glu
165 170 175

Leu Val Glu Lys Gly Lys Ser Leu Gly Ala Lys Arg Val Met Pro Leu
180 185 190

Ala Val Ser Gly Pro Phe His Ser Ser Leu Met Lys Val Ile Glu Glu
195 200 205

Asp Phe Ser Ser Tyr Ile Asn Gln Phe Glu Trp Arg Asp Ala Lys Phe
210 215 220

Pro Val Val Gln Asn Val Asn Ala Gln Gly Glu Thr Asp Lys Glu Val
225 230 235 240

Ile Lys Ser Asn Met Val Lys Gln Leu Tyr Ser Pro Val Gln Phe Ile
245 250 255

Asn Ser Thr Glu Trp Leu Ile Asp Gln Gly Val Asp His Phe Ile Glu
260 265 270

Ile Gly Pro Gly Lys Val Leu Ser Gly Leu Ile Lys Lys Ile Asn Arg
275 280 285

Asp Val Lys Leu Thr Ser Ile Gln Thr Leu Glu Asp Val Lys Gly Trp
290 295 300

Asn Glu Asn Asp
305

<210> 17
<211> 1080
<212> DNA
<213> Staphylococcus aureus

<400> 17
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agaaatgtta attgatgcaa aagaaaatgg ttatgcggta ggtcaataca atattaataa 180
cctagaattc actcaagcaa ttttagaagc gtcacaagaa gaaaatgcac ctgtaatttt 240
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tgaagggtta atgcatgact taaacatcac tattcctgta gcaatccatt tagaccatgg 360
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tgcttcacac agcccattcg aagaaaacgt agcaacaact aaaaaagttg ttgaatacgc 480
tcatgaaaaa ggtgtttctg tagaagctga attaggtact gttggtggac aagaagatga 540
tgttgtagca gacggcatca tttatgctga tcctaaagaa tgtcaagaac tagttgaaaa 600
aactggtatt gatgcattag cgccagcatt aggttcagtt catggtccat acaaaggtga 660
accaaaatta ggatttaaag aaatggaaga aatcggttta tctacaggtt taccattagt 720
attacacggt ggtactggta tcccgactaa agatatccaa aaagcaattc catttggtac 780
agctaaaatt aacgtaaaca ctgaaaacca aatcgcttca gcaaaagcag ttcgtgacgt 840
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catcaaagaa acagttaaag gtaaaattaa agagttcggt acttctaacc gcgctaaata 960
attaatattt agtctttaag ttattaataa cgtagggata ttaattttaa aagaagcaga 1020
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<210> 18
<211> 286
<212> PRT
<213> Staphylococcus aureus

<400> 18
Met Pro Leu Val Ser Met Lys Glu Met Leu Ile Asp Ala Lys Glu Asn
1 5 10 15

Gly Tyr Ala Val Gly Gln Tyr Asn Ile Asn Asn Leu Glu Phe Thr Gln
20 25 30

Ala Ile Leu Glu Ala Ser Gln Glu Glu Asn Ala Pro Val Ile Leu Gly
35 40 45

Val Ser Glu Gly Ala Ala Arg Tyr Met Ser Gly Phe Tyr Thr Ile Val
50 55 60

Lys Met Val Glu Gly Leu Met His Asp Leu Asn Ile Thr Ile Pro Val
65 70 75 80

Ala Ile His Leu Asp His Gly Ser Ser Phe Glu Lys Cys Lys Glu Ala
85 90 95

Ile Asp Ala Gly Phe Thr Ser Val Met Ile Asp Ala Ser His Ser Pro
100 105 110

Phe Glu Glu Asn Val Ala Thr Thr Lys Lys Val Val Glu Tyr Ala His

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        115                 120                 125

Glu Lys Gly Val Ser Val Glu Ala Glu Leu Gly Thr Val Gly Gly Gln
    130                 135                 140

Glu Asp Asp Val Val Ala Asp Gly Ile Ile Tyr Ala Asp Pro Lys Glu
145                 150                 155                 160

Cys Gln Glu Leu Val Glu Lys Thr Gly Ile Asp Ala Leu Ala Pro Ala
                165                 170                 175

Leu Gly Ser Val His Gly Pro Tyr Lys Gly Glu Pro Lys Leu Gly Phe
            180                 185                 190

Lys Glu Met Glu Glu Ile Gly Leu Ser Thr Gly Leu Pro Leu Val Leu
        195                 200                 205

His Gly Gly Thr Gly Ile Pro Thr Lys Asp Ile Gln Lys Ala Ile Pro
    210                 215                 220

Phe Gly Thr Ala Lys Ile Asn Val Asn Thr Glu Asn Gln Ile Ala Ser
225                 230                 235                 240

Ala Lys Ala Val Arg Asp Val Leu Asn Asn Asp Lys Glu Val Tyr Asp
                245                 250                 255

Pro Arg Lys Tyr Leu Gly Pro Ala Arg Glu Ala Ile Lys Glu Thr Val
            260                 265                 270

Lys Gly Lys Ile Lys Glu Phe Gly Thr Ser Asn Arg Ala Lys
        275                 280                 285


<210> 19
<211> 1340
<212> DNA
<213> Staphylococcus aureus

<400> 19
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acgactttta aattactatc aaaattgcca aacaagaatc taatttattt tgaaagcttt 180
catggtaaac aatacagcga caaccccaaa gcattatatg aatacttaac tgaacatagc 240
gatgcccaat taatatgggg tgtgaaaaaa ggatatgaac acatattcca acagcacaat 300
gtaccatatg ttacaaagtt ttcaatgaaa tggtttttag cgatgccaag agcgaaagcg 360
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caaacatggc atggcacgcc attaaaaaag attggtttgg atattagtaa cgttaaaatg 480
ctaggaacaa atactcaaaa ttaccaagat ggctttaaaa aagaaagcca acggtgggat 540
tatctagtgt cacctaatcc atattcgaca tcgatatttc aaaatgcatt tcatgttagt 600
cgagataaga ttttggaaac aggttatcca agaaatgata aattatcaca taaacgcaat 660
gatactgaat atattaatgg tattaagaca agattaaata ttccattaga taaaaaagtg 720
attatgtacg cgccaacttg gcgtgacgat gaagcgattc gagaaggttc atatcaattt 780
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gatggacaag cgtcacaacg aatttgccaa acgattttta agtgataact taaaaacaat 1260
aaaaaattat aaattaatta gttaagtgat ataaataata aacgaaatgt ttgcttgtat 1320
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gttattattt gtgtatgaaa 1340

<210> 20
<211> 389
<212> PRT
<213> Staphylococcus aureus

<400> 20
Met Ile Lys Asn Thr Ile Lys Lys Leu Ile Glu His Ser Ile Tyr Thr
1 5 10 15

Thr Phe Lys Leu Leu Ser Lys Leu Pro Asn Lys Asn Leu Ile Tyr Phe
20 25 30

Glu Ser Phe His Gly Lys Gln Tyr Ser Asp Asn Pro Lys Ala Leu Tyr
35 40 45

Glu Tyr Leu Thr Glu His Ser Asp Ala Gln Leu Ile Trp Gly Val Lys
50 55 60

Lys Gly Tyr Glu His Ile Phe Gln Gln His Asn Val Pro Tyr Val Thr
65 70 75 80

Lys Phe Ser Met Lys Trp Phe Leu Ala Met Pro Arg Ala Lys Ala Trp
85 90 95

Met Ile Asn Thr Arg Thr Pro Asp Trp Leu Tyr Lys Ser Pro Arg Thr
100 105 110

Thr Tyr Leu Gln Thr Trp His Gly Thr Pro Leu Lys Lys Ile Gly Leu
115 120 125

Asp Ile Ser Asn Val Lys Met Leu Gly Thr Asn Thr Gln Asn Tyr Gln
130 135 140

Asp Gly Phe Lys Lys Glu Ser Gln Arg Trp Asp Tyr Leu Val Ser Pro
145 150 155 160

Asn Pro Tyr Ser Thr Ser Ile Phe Gln Asn Ala Phe His Val Ser Arg
165 170 175

Asp Lys Ile Leu Glu Thr Gly Tyr Pro Arg Asn Asp Lys Leu Ser His
180 185 190

Lys Arg Asn Asp Thr Glu Tyr Ile Asn Gly Ile Lys Thr Arg Leu Asn
195 200 205

Ile Pro Leu Asp Lys Lys Val Ile Met Tyr Ala Pro Thr Trp Arg Asp
210 215 220

Asp Glu Ala Ile Arg Glu Gly Ser Tyr Gln Phe Asn Val Asn Phe Asp
225 230 235 240

Ile Glu Ala Leu Arg Gln Ala Leu Asp Asp Asp Tyr Val Ile Leu Leu
245 250 255

Arg Met His Tyr Leu Val Val Thr Arg Ile Asp Glu His Asp Asp Phe
260 265 270

Val Lys Asp Val Ser Asp Tyr Glu Asp Ile Ser Asp Leu Tyr Leu Ile
275 280 285

Ser Asp Ala Leu Val Thr Asp Tyr Ser Ser Val Met Phe Asp Phe Gly
290 295 300

Val Leu Lys Arg Pro Gln Ile Phe Tyr Ala Tyr Asp Leu Asp Lys Tyr
305 310 315 320

Gly Asp Glu Leu Arg Gly Phe Tyr Met Asp Tyr Lys Lys Glu Leu Pro
325 330 335

Gly Pro Ile Val Glu Asn Gln Thr Ala Leu Ile Asp Ala Leu Lys Gln
340 345 350

Ile Asp Glu Thr Ala Asn Glu Tyr Ile Glu Ala Arg Thr Val Phe Tyr
355 360 365

Gln Lys Phe Cys Ser Leu Glu Asp Gly Gln Ala Ser Gln Arg Ile Cys
370 375 380

Gln Thr Ile Phe Lys
385

<210> 21
<211> 1430
<212> DNA
<213> Staphylococcus aureus

<400> 21
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atattgacag catctttatt agcttctgat aaaccgagca aattagttaa tgttccagct 240
ttaagtgatg tagaaacaat aaataatgta ttaacaactt taaatgctga cgttacatac 300
aaaaaggacg aaaatgctgt tgtcgttgat gcaacaaaga ctctaaatga agaggcacca 360
tatgaatatg ttagtaaaat gcgtgcaagt attttagtta tgggacctct tttagcaaga 420
ctaggacatg ctattgttgc attgcctggt ggttgtgcaa ttggaagtag accgattgag 480
caacacatta aaggttttga agctttaggc gcagaaattc atcttgaaaa tggtaatatt 540
tatgctaatg ctaaagatgg attaaaaggt acatcaattc atttagattt tccaagtgta 600
ggagcaacac aaaatattat tatggcagca tcattagcta agggtaagac tttaattgaa 660
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agaattactg gtgctggtac agacacaatt acaatcaatg gtgtagaatc attacatggt 780
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<210> 22
<211> 421
<212> PRT
<213> Staphylococcus aureus

<400> 22
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            20                  25                  30

Leu Leu Ala Ser Asp Lys Pro Ser Lys Leu Val Asn Val Pro Ala Leu
        35                  40                  45

Ser Asp Val Glu Thr Ile Asn Asn Val Leu Thr Thr Leu Asn Ala Asp
    50                  55                  60

Val Thr Tyr Lys Lys Asp Glu Asn Ala Val Val Val Asp Ala Thr Lys
65                  70                  75                  80

Thr Leu Asn Glu Glu Ala Pro Tyr Glu Tyr Val Ser Lys Met Arg Ala
                85                  90                  95

Ser Ile Leu Val Met Gly Pro Leu Leu Ala Arg Leu Gly His Ala Ile
            100                 105                 110

Val Ala Leu Pro Gly Gly Cys Ala Ile Gly Ser Arg Pro Ile Glu Gln
        115                 120                 125

His Ile Lys Gly Phe Glu Ala Leu Gly Ala Glu Ile His Leu Glu Asn
    130                 135                 140

Gly Asn Ile Tyr Ala Asn Ala Lys Asp Gly Leu Lys Gly Thr Ser Ile
145                 150                 155                 160

His Leu Asp Phe Pro Ser Val Gly Ala Thr Gln Asn Ile Ile Met Ala
                165                 170                 175

Ala Ser Leu Ala Lys Gly Lys Thr Leu Ile Glu Asn Ala Ala Lys Glu
            180                 185                 190

Pro Glu Ile Val Asp Leu Ala Asn Tyr Ile Asn Glu Met Gly Gly Arg
        195                 200                 205

Ile Thr Gly Ala Gly Thr Asp Thr Ile Thr Ile Asn Gly Val Glu Ser
    210                 215                 220

Leu His Gly Val Glu His Ala Ile Ile Pro Asp Arg Ile Glu Ala Gly
225                 230                 235                 240

Thr Leu Leu Ile Ala Gly Ala Ile Thr Arg Gly Asp Ile Phe Val Arg
                245                 250                 255

Gly Ala Ile Lys Glu His Met Ala Ser Leu Val Tyr Lys Leu Glu Glu
            260                 265                 270

Met Gly Val Glu Leu Asp Tyr Gln Glu Asp Gly Ile Arg Val Arg Ala
        275                 280                 285

Glu Gly Glu Leu Gln Pro Val Asp Ile Lys Thr Leu Pro His Pro Gly
    290                 295                 300

Phe Pro Thr Asp Met Gln Ser Gln Met Met Ala Leu Leu Leu Thr Ala
305                 310                 315                 320

Asn Gly His Lys Val Val Thr Glu Thr Val Phe Glu Asn Arg Phe Met
                325                 330                 335
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His Val Ala Glu Phe Lys Arg Met Asn Ala Asn Ile Asn Val Glu Gly
340 345 350

Arg Ser Ala Lys Leu Glu Gly Lys Ser Gln Leu Gln Gly Ala Gln Val
355 360 365

Lys Ala Thr Asp Leu Arg Ala Ala Ala Ala Leu Ile Leu Ala Gly Leu
370 375 380

Val Ala Asp Gly Lys Thr Ser Val Thr Glu Leu Thr His Leu Asp Arg
385 390 395 400

Gly Tyr Val Asp Leu His Gly Lys Leu Lys Gln Leu Gly Ala Asp Ile
405 410 415

Glu Arg Ile Asn Asp
420

<210> 23
<211> 2204
<212> DNA
<213> Staphylococcus aureus

<400> 23
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tgtgaacgag ttacatgatt tattaaatca atacagttat gaatactatg tagaggataa 180
tccatctgta ccagatagtg aatatgacaa attacttcat gaactgatta aaatagaaga 240
ggagcatcct gagtataaga ctgtagattc tccaacagtt agagttggcg gtgaagccca 300
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tgaggatgat ttgagaaaat tcgaccaacg catacgtgaa caaattggca acgttgaata 420
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cgttcaaggt ttaacacgtg gtgatggaac aacaggtgaa gatattaccg aaaatttaaa 540
aacaattcat gcgatacctt tgaaaatgaa agaaccatta aatgtagaag ttcgtggtga 600
agcatatatg ccgagacgtt catttttacg attaaatgaa gaaaaagaaa aaaatgatga 660
gcagttattt gcaaatccaa gaaacgctgc tgcgggatca ttaagacagt tagattctaa 720
attaacggca aaacgaaagc taagcgtatt tatatatagt gtcaatgatt tcactgattt 780
caatgcgcgt tcgcaaagtg aagcattaga tgagttagat aaattaggtt ttacaacgaa 840
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aagccaaaga gagtcattac cttatgatat tgatgggatt gttattaagg ttaatgattt 960
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aagagcatct ttgcacaatg aggatttaat tcatgacaga gatattcgaa ttggtgatag 1200
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<210> 24
<211> 667
<212> PRT
<213> Staphylococcus aureus

<400> 24
Met Ala Asp Leu Ser Ser Arg Val Asn Glu Leu His Asp Leu Leu Asn
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Gln Tyr Ser Tyr Glu Tyr Tyr Val Glu Asp Asn Pro Ser Val Pro Asp
20 25 30

Ser Glu Tyr Asp Lys Leu Leu His Glu Leu Ile Lys Ile Glu Glu Glu
35 40 45

His Pro Glu Tyr Lys Thr Val Asp Ser Pro Thr Val Arg Val Gly Gly
50 55 60

Glu Ala Gln Ala Ser Phe Asn Lys Val Asn His Asp Thr Pro Met Leu
65 70 75 80

Ser Leu Gly Asn Ala Phe Asn Glu Asp Asp Leu Arg Lys Phe Asp Gln
85 90 95

Arg Ile Arg Glu Gln Ile Gly Asn Val Glu Tyr Met Cys Glu Leu Lys
100 105 110

Ile Asp Gly Leu Ala Val Ser Leu Lys Tyr Val Asp Gly Tyr Phe Val
115 120 125

Gln Gly Leu Thr Arg Gly Asp Gly Thr Thr Gly Glu Asp Ile Thr Glu
130 135 140

Asn Leu Lys Thr Ile His Ala Ile Pro Leu Lys Met Lys Glu Pro Leu
145 150 155 160

Asn Val Glu Val Arg Gly Glu Ala Tyr Met Pro Arg Arg Ser Phe Leu
165 170 175

Arg Leu Asn Glu Glu Lys Glu Lys Asn Asp Glu Gln Leu Phe Ala Asn
180 185 190

Pro Arg Asn Ala Ala Ala Gly Ser Leu Arg Gln Leu Asp Ser Lys Leu
195 200 205

Thr Ala Lys Arg Lys Leu Ser Val Phe Ile Tyr Ser Val Asn Asp Phe
210 215 220

Thr Asp Phe Asn Ala Arg Ser Gln Ser Glu Ala Leu Asp Glu Leu Asp
225 230 235 240

Lys Leu Gly Phe Thr Thr Asn Lys Asn Arg Ala Arg Val Asn Asn Ile
245 250 255

Asp Gly Val Leu Glu Tyr Ile Glu Lys Trp Thr Ser Gln Arg Glu Ser
260 265 270

Leu Pro Tyr Asp Ile Asp Gly Ile Val Ile Lys Val Asn Asp Leu Asp

275 280 285

Gln Gln Asp Glu Met Gly Phe Thr Gln Lys Ser Pro Arg Trp Ala Ile
290 295 300

Ala Tyr Lys Phe Pro Ala Glu Glu Val Val Thr Lys Leu Leu Asp Ile
305 310 315 320

Glu Leu Ser Ile Gly Arg Thr Gly Val Val Thr Pro Thr Ala Ile Leu
325 330 335

Glu Pro Val Lys Val Ala Gly Thr Thr Val Ser Arg Ala Ser Leu His
340 345 350

Asn Glu Asp Leu Ile His Asp Arg Asp Ile Arg Ile Gly Asp Ser Val
355 360 365

Val Val Lys Lys Ala Gly Asp Ile Ile Pro Glu Val Val Arg Ser Ile
370 375 380

Pro Glu Arg Arg Pro Glu Asp Ala Val Thr Tyr His Met Pro Thr His
385 390 395 400

Cys Pro Ser Cys Gly His Glu Leu Val Arg Ile Glu Gly Glu Val Ala
405 410 415

Leu Arg Cys Ile Asn Pro Lys Cys Gln Ala Gln Leu Val Glu Gly Leu
420 425 430

Ile His Phe Val Ser Arg Gln Ala Met Asn Ile Asp Gly Leu Gly Thr
435 440 445

Lys Ile Ile Gln Gln Leu Tyr Gln Ser Glu Leu Ile Lys Asp Val Ala
450 455 460

Asp Ile Phe Tyr Leu Thr Glu Glu Asp Leu Leu Pro Leu Asp Arg Met
465 470 475 480

Gly Gln Lys Lys Val Asp Asn Leu Leu Ala Ala Ile Gln Gln Ala Lys
485 490 495

Asp Asn Ser Leu Glu Asn Leu Leu Phe Gly Leu Gly Ile Arg His Leu
500 505 510

Gly Val Lys Ala Ser Gln Val Leu Ala Glu Lys Tyr Glu Thr Ile Asp
515 520 525

Arg Leu Leu Thr Val Thr Glu Ala Glu Leu Val Glu Ile His Asp Ile
530 535 540

Gly Asp Lys Val Ala Gln Ser Val Val Thr Tyr Leu Glu Asn Glu Asp
545 550 555 560

Ile Arg Ala Leu Ile Gln Lys Leu Lys Asp Lys His Val Asn Met Ile
565 570 575

Tyr Lys Gly Ile Lys Thr Ser Asp Ile Glu Gly His Pro Glu Phe Ser
580 585 590

Gly Lys Thr Ile Val Leu Thr Gly Lys Leu His Gln Met Thr Arg Asn
595 600 605

Glu Ala Ser Lys Trp Leu Ala Ser Gln Gly Ala Lys Val Thr Ser Ser
610 615 620

Val Thr Lys Asn Thr Asp Val Val Ile Ala Gly Glu Asp Ala Gly Ser
625 630 635 640

Lys Leu Thr Lys Ala Gln Ser Leu Gly Ile Glu Ile Trp Thr Glu Gln
645 650 655

Gln Phe Val Asp Lys Gln Asn Glu Leu Asn Ser
660 665

<210> 25
<211> 959
<212> DNA
<213> Staphylococcus aureus

<400> 25
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agctgcaacc aaaccaggta tcactacgaa agagcttgat aatattgcga aagagttatt 240
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tattagtgtc aatgaagagg tggcacatgg gattccaagt aagcgtgtca ttcgtgaagg 360
agatttagta aatattgatg tatcggcttt gaagaatggc tattatgcag atacaggcat 420
ttcatttgtc gttggagaat cagatgatcc aatgaaacaa aaagtatgtg acgtagcaac 480
gatggcattt gagaatgcaa ttgcaaaagt aaaaccgggt actaagttaa gtaacattgg 540
taaagcggtg cataatacag ctagacaaaa tgatttgaaa gtcattaaaa acttaacagg 600
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<210> 26
<211> 252
<212> PRT
<213> Staphylococcus aureus

<400> 26
Met Ile Val Lys Thr Glu Glu Glu Leu Gln Ala Leu Lys Glu Ile Gly
1 5 10 15

Tyr Ile Cys Ala Lys Val Arg Asn Thr Met Gln Ala Ala Thr Lys Pro
20 25 30

Gly Ile Thr Thr Lys Glu Leu Asp Asn Ile Ala Lys Glu Leu Phe Glu
35 40 45

Glu Tyr Gly Ala Ile Ser Ala Pro Ile His Asp Glu Asn Phe Pro Gly
50 55 60

Gln Thr Cys Ile Ser Val Asn Glu Glu Val Ala His Gly Ile Pro Ser
65 70 75 80

Lys Arg Val Ile Arg Glu Gly Asp Leu Val Asn Ile Asp Val Ser Ala
85 90 95

Leu Lys Asn Gly Tyr Tyr Ala Asp Thr Gly Ile Ser Phe Val Val Gly
100 105 110

Glu Ser Asp Asp Pro Met Lys Gln Lys Val Cys Asp Val Ala Thr Met
115 120 125

Ala Phe Glu Asn Ala Ile Ala Lys Val Lys Pro Gly Thr Lys Leu Ser
130 135 140

Asn Ile Gly Lys Ala Val His Asn Thr Ala Arg Gln Asn Asp Leu Lys
145 150 155 160

Val Ile Lys Asn Leu Thr Gly His Gly Val Gly Leu Ser Leu His Glu
165 170 175

Ala Pro Ala His Val Leu Asn Tyr Phe Asp Pro Lys Asp Lys Thr Leu
180 185 190

Leu Thr Glu Gly Met Val Leu Ala Ile Glu Pro Phe Ile Ser Ser Asn
195 200 205

Ala Ser Phe Val Thr Glu Gly Lys Asn Glu Trp Ala Phe Glu Thr Ser
210 215 220

Asp Lys Ser Phe Val Ala Gln Ile Glu His Thr Val Ile Val Thr Lys
225 230 235 240

Asp Gly Pro Ile Leu Thr Thr Lys Ile Glu Glu Glu
245 250

<210> 27
<211> 3400
<212> DNA
<213> Staphylococcus aureus

<400> 27
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gaagaaatgg ccaacacatt agaaagcatt ttagattttg caaaacaaaa tgatagcgct 240
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ctacgaatcg gttgagaatt tattaacttt aataaaagac aaaaaaatca aaccatctga 480
tgttgttaaa gatatatatg atgcaattga agagactgat ccaacaatta agtcttttct 540
agcgctggat aaagaaaatg caatcaaaaa agcgcaagaa ttggatgaat tacaagcaaa 600
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tggtattcca tcatattacg tgattgcatc atcagaagct tcgtcaaacc tttctcgttt 1380
tgacggaatt cgttatggtt atcattctaa agaagctcat tcattagaag aattatataa 1440

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<210> 28
<211> 485
<212> PRT
<213> Staphylococcus aureus

<400> 28

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Met Ser Ile Arg Tyr Glu Ser Val Glu Asn Leu Leu Thr Leu Ile Lys
1               5                   10                  15

Asp Lys Lys Ile Lys Pro Ser Asp Val Val Lys Asp Ile Tyr Asp Ala
            20                  25                  30

Ile Glu Glu Thr Asp Pro Thr Ile Lys Ser Phe Leu Ala Leu Asp Lys
        35                  40                  45

Glu Asn Ala Ile Lys Lys Ala Gln Glu Leu Asp Glu Leu Gln Ala Lys
    50                  55                  60

Asp Gln Met Asp Gly Lys Leu Phe Gly Ile Pro Met Gly Ile Lys Asp
65                  70                  75                  80

Asn Ile Ile Thr Asn Gly Leu Glu Thr Thr Cys Ala Ser Lys Met Leu
                85                  90                  95

Glu Gly Phe Val Pro Ile Tyr Glu Ser Thr Val Met Glu Lys Leu His
            100                 105                 110
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Asn Glu Asn Ala Val Leu Ile Gly Lys Leu Asn Met Asp Glu Phe Ala
        115                 120                 125

Met Gly Gly Ser Thr Glu Thr Ser Tyr Phe Lys Lys Thr Val Asn Pro
    130                 135                 140

Phe Asp His Lys Ala Val Pro Gly Gly Ser Ser Gly Gly Ser Ala Ala
145                 150                 155                 160

Ala Val Ala Ala Gly Leu Val Pro Phe Ser Leu Gly Ser Asp Thr Gly
                165                 170                 175

Gly Ser Ile Arg Gln Pro Ala Ala Tyr Cys Gly Val Val Gly Met Lys
            180                 185                 190

Pro Thr Tyr Gly Arg Val Ser Arg Phe Gly Leu Val Ala Phe Ala Ser
        195                 200                 205

Ser Leu Asp Gln Ile Gly Pro Leu Thr Arg Asn Val Lys Asp Asn Ala
    210                 215                 220

Ile Val Leu Glu Ala Ile Ser Gly Ala Asp Val Asn Asp Ser Thr Ser
225                 230                 235                 240

Ala Pro Val Asp Asp Val Asp Phe Thr Ser Glu Ile Gly Lys Asp Ile
                245                 250                 255

Lys Gly Leu Lys Val Ala Leu Pro Lys Glu Tyr Leu Gly Glu Gly Val
            260                 265                 270

Ala Asp Asp Val Lys Glu Ala Val Gln Asn Ala Val Glu Thr Leu Lys
        275                 280                 285

Ser Leu Gly Ala Val Val Glu Glu Val Ser Leu Pro Asn Thr Lys Phe
    290                 295                 300

Gly Ile Pro Ser Tyr Tyr Val Ile Ala Ser Ser Glu Ala Ser Ser Asn
305                 310                 315                 320

Leu Ser Arg Phe Asp Gly Ile Arg Tyr Gly Tyr His Ser Lys Glu Ala
                325                 330                 335

His Ser Leu Glu Glu Leu Tyr Lys Met Ser Arg Ser Glu Gly Phe Gly
            340                 345                 350

Lys Glu Val Lys Arg Arg Ile Phe Leu Gly Thr Phe Ala Leu Ser Ser
        355                 360                 365

Gly Tyr Tyr Asp Ala Tyr Tyr Lys Lys Ser Gln Lys Val Arg Thr Leu
    370                 375                 380

Ile Lys Asn Asp Phe Asp Lys Val Phe Glu Asn Tyr Asp Val Val Val
385                 390                 395                 400

Gly Pro Thr Ala Pro Thr Thr Ala Phe Asn Leu Gly Glu Glu Ile Asp
                405                 410                 415

Asp Pro Leu Thr Met Tyr Ala Asn Asp Leu Leu Thr Thr Pro Val Asn
            420                 425                 430

Leu Ala Gly Leu Pro Gly Ile Ser Val Pro Cys Gly Gln Ser Asn Gly
```

435 440 445

Arg Pro Ile Gly Leu Gln Phe Ile Gly Lys Pro Phe Asp Glu Lys Thr
450 455 460

Leu Tyr Arg Val Ala Tyr Gln Tyr Glu Thr Gln Tyr Asn Leu His Asp
465 470 475 480

Val Tyr Glu Lys Leu
485

<210> 29
<211> 475
<212> PRT
<213> Staphylococcus aureus

<400> 29
Met His Phe Glu Thr Val Ile Gly Leu Glu Val His Val Glu Leu Lys
1 5 10 15

Thr Asp Ser Lys Met Phe Ser Pro Ser Pro Ala His Phe Gly Ala Glu
20 25 30

Pro Asn Ser Asn Thr Asn Val Ile Asp Leu Ala Tyr Pro Gly Val Leu
35 40 45

Pro Val Val Asn Lys Arg Ala Val Asp Trp Ala Met Arg Ala Ala Met
50 55 60

Ala Leu Asn Met Glu Ile Ala Thr Glu Ser Lys Phe Asp Arg Lys Asn
65 70 75 80

Tyr Phe Tyr Pro Asp Asn Pro Lys Ala Tyr Gln Ile Ser Gln Phe Asp
85 90 95

Gln Pro Ile Gly Glu Asn Gly Tyr Ile Asp Ile Glu Val Asp Gly Glu
100 105 110

Thr Lys Arg Ile Gly Ile Thr Arg Leu His Met Glu Glu Asp Ala Gly
115 120 125

Lys Ser Thr His Lys Gly Glu Tyr Ser Leu Val Asp Leu Asn Arg Gln
130 135 140

Gly Thr Pro Leu Ile Glu Ile Val Ser Glu Pro Asp Ile Arg Ser Pro
145 150 155 160

Lys Glu Ala Tyr Ala Tyr Leu Glu Lys Leu Arg Ser Ile Ile Gln Tyr
165 170 175

Thr Gly Val Ser Asp Val Lys Met Glu Glu Gly Ser Leu Arg Cys Asp
180 185 190

Ala Asn Ile Ser Leu Arg Pro Tyr Gly Gln Glu Lys Phe Gly Thr Lys
195 200 205

Ala Glu Leu Lys Asn Leu Asn Ser Phe Asn Tyr Val Arg Lys Gly Leu
210 215 220

Glu Tyr Glu Glu Lys Arg Gln Glu Glu Glu Leu Leu Asn Gly Gly Glu

225 230 235 240

Ile Gly Gln Glu Thr Arg Arg Phe Asp Glu Ser Thr Gly Lys Thr Ile
245 250 255

Leu Met Arg Val Lys Glu Gly Ser Asp Asp Tyr Arg Tyr Phe Pro Glu
260 265 270

Pro Asp Ile Val Pro Leu Tyr Ile Asp Asp Ala Trp Lys Glu Arg Val
275 280 285

Arg Gln Thr Ile Pro Glu Leu Pro Asp Glu Arg Lys Ala Lys Tyr Val
290 295 300

Asn Glu Leu Gly Leu Pro Ala Tyr Asp Ala His Val Leu Thr Leu Thr
305 310 315 320

Lys Glu Met Ser Asp Phe Phe Glu Ser Thr Ile Glu His Gly Ala Asp
325 330 335

Val Lys Leu Thr Ser Asn Trp Leu Met Gly Gly Val Asn Glu Tyr Leu
340 345 350

Asn Lys Asn Gln Val Glu Leu Leu Asp Thr Lys Leu Thr Pro Glu Asn
355 360 365

Leu Ala Gly Met Ile Lys Leu Ile Glu Asp Gly Thr Met Ser Ser Lys
370 375 380

Ile Ala Lys Lys Val Phe Pro Glu Leu Ala Ala Lys Gly Gly Asn Ala
385 390 395 400

Lys Gln Ile Met Glu Asp Asn Gly Leu Val Gln Ile Ser Asp Glu Ala
405 410 415

Thr Leu Leu Lys Phe Val Asn Glu Ala Leu Asp Asn Asn Glu Gln Ser
420 425 430

Val Glu Asp Tyr Lys Asn Gly Lys Gly Lys Ala Met Gly Phe Leu Val
435 440 445

Gly Gln Ile Met Lys Ala Ser Lys Gly Gln Ala Asn Pro Gln Leu Val
450 455 460

Asn Gln Leu Leu Lys Gln Glu Leu Asp Lys Arg
465 470 475

<210> 30
<211> 100
<212> PRT
<213> Staphylococcus aureus

<400> 30
Met Thr Lys Val Thr Arg Glu Glu Val Glu His Ile Ala Asn Leu Ala
1 5 10 15

Arg Leu Gln Ile Ser Pro Glu Glu Thr Glu Glu Met Ala Asn Thr Leu
20 25 30

Glu Ser Ile Leu Asp Phe Ala Lys Gln Asn Asp Ser Ala Asp Thr Glu

35 40 45

Gly Val Glu Pro Thr Tyr His Val Leu Asp Leu Gln Asn Val Leu Arg
50 55 60

Glu Asp Lys Ala Ile Lys Gly Ile Pro Gln Glu Leu Ala Leu Lys Asn
65 70 75 80

Ala Lys Glu Thr Glu Asp Gly Gln Phe Lys Val Pro Thr Ile Met Asn
85 90 95

Glu Glu Asp Ala
100

<210> 31
<211> 772
<212> DNA
<213> Staphylococcus aureus

<400> 31
cttactaagc taaagaataa tgataattga tggcaatggc ggaaaatgga tgttgtcatt 60
ataataataa atgaaacaat tatgttggag gtaaacacgc atgaaatgta ttgtaggtct 120
aggtaatata ggtaaacgtt ttgaacttac aagacataat atcggctttg aagtcgttga 180
ttatatttta gagaaaaata atttttcatt agataaacaa aagtttaaag gtgcatatac 240
aattgaacga atgaacggcg ataaagtgtt atttatcgaa ccaatgacaa tgatgaattt 300
gtcaggtgaa gcagttgcac cgattatgga ttattacaat gttaatccag aagatttaat 360
tgtcttatat gatgatttag atttagaaca aggacaagtt cgcttaagac aaaaaggaag 420
tgcgggcggt cacaatggta tgaaatcaat tattaaaatg cttggtacag accaatttaa 480
acgtattcgt attggtgtgg gaagaccaac gaatggtatg acggtacctg attatgtttt 540
acaacgcttt tcaaatgatg aaatggtaac gatggaaaaa gttatcgaac acgcagcacg 600
cgcaattgaa aagtttgttg aaacatcacg atttgaccat gttatgaatg aatttaatgg 660
tgaagtgaaa taatgacaat attgacaacg cttataaaag aagataatca ttttcaagac 720
cttaatcagg tatttggaca agcaaacaca ctagtaactg gtctttcccc gt 772

<210> 32
<211> 190
<212> PRT
<213> Staphylococcus aureus

<400> 32
Met Lys Cys Ile Val Gly Leu Gly Asn Ile Gly Lys Arg Phe Glu Leu
1 5 10 15

Thr Arg His Asn Ile Gly Phe Glu Val Val Asp Tyr Ile Leu Glu Lys
20 25 30

Asn Asn Phe Ser Leu Asp Lys Gln Lys Phe Lys Gly Ala Tyr Thr Ile
35 40 45

Glu Arg Met Asn Gly Asp Lys Val Leu Phe Ile Glu Pro Met Thr Met
50 55 60

Met Asn Leu Ser Gly Glu Ala Val Ala Pro Ile Met Asp Tyr Tyr Asn
65 70 75 80

Val Asn Pro Glu Asp Leu Ile Val Leu Tyr Asp Asp Leu Asp Leu Glu
85 90 95

Gln Gly Gln Val Arg Leu Arg Gln Lys Gly Ser Ala Gly Gly His Asn
100 105 110

Gly Met Lys Ser Ile Ile Lys Met Leu Gly Thr Asp Gln Phe Lys Arg
115 120 125

Ile Arg Ile Gly Val Gly Arg Pro Thr Asn Gly Met Thr Val Pro Asp
130 135 140

Tyr Val Leu Gln Arg Phe Ser Asn Asp Glu Met Val Thr Met Glu Lys
145 150 155 160

Val Ile Glu His Ala Ala Arg Ala Ile Glu Lys Phe Val Glu Thr Ser
165 170 175

Arg Phe Asp His Val Met Asn Glu Phe Asn Gly Glu Val Lys
180 185 190

<210> 33
<211> 1277
<212> PRT
<213> Staphylococcus aureus

<400> 33
Thr Gly Ala Thr Cys Cys Gly Ala Thr Thr Ala Thr Cys Thr Thr Ala
1 5 10 15

Gly Thr Ala Gly Gly Thr Gly Cys Cys Ala Ala Thr Gly Ala Ala Ala
20 25 30

Gly Thr Thr Ala Thr Gly Ala Gly Cys Cys Ala Cys Gly Thr Thr Gly
35 40 45

Thr Cys Gly Cys Gly Cys Gly Cys Ala Cys Cys Ala Thr Ala Thr Cys
50 55 60

Gly Thr Ala Gly Cys Ala Cys Cys Thr Ala Gly Thr Gly Ala Thr Ala
65 70 75 80

Ala Thr Ala Ala Thr Ala Ala Gly Gly Ala Gly Gly Ala Ala Thr Thr
85 90 95

Ala Thr Ala Ala Gly Thr Gly Thr Thr Thr Gly Ala Thr Cys Ala Ala
100 105 110

Thr Thr Ala Gly Ala Thr Ala Thr Thr Gly Thr Ala Gly Ala Ala Gly
115 120 125

Ala Ala Ala Gly Ala Thr Ala Cys Gly Ala Ala Cys Ala Gly Thr Thr
130 135 140

Ala Ala Ala Thr Gly Ala Ala Cys Thr Gly Thr Thr Ala Ala Gly Thr
145 150 155 160

Gly Ala Cys Cys Cys Ala Gly Ala Thr Gly Thr Thr Gly Thr Ala Ala
165 170 175

Ala Thr Gly Ala Thr Thr Cys Ala Gly Ala Thr Ala Ala Ala Thr Thr
180 185 190

Ala Cys Gly Thr Ala Ala Ala Thr Ala Thr Thr Cys Thr Ala Ala Ala
195 200 205

Gly Ala Gly Cys Ala Ala Gly Cys Thr Gly Ala Thr Thr Thr Ala Cys
210 215 220

Ala Ala Ala Ala Ala Ala Cys Thr Gly Thr Ala Gly Ala Thr Gly Thr
225 230 235 240

Thr Thr Ala Thr Cys Gly Thr Ala Ala Cys Thr Ala Thr Ala Ala Ala
245 250 255

Gly Cys Thr Ala Ala Ala Ala Ala Ala Gly Ala Ala Gly Ala Ala Thr
260 265 270

Thr Ala Gly Cys Thr Gly Ala Thr Ala Thr Thr Gly Ala Ala Gly Ala
275 280 285

Ala Ala Thr Gly Thr Thr Ala Ala Gly Thr Gly Ala Gly Ala Cys Thr
290 295 300

Gly Ala Thr Gly Ala Thr Ala Ala Ala Gly Ala Ala Gly Ala Ala Gly
305 310 315 320

Thr Ala Gly Ala Ala Ala Thr Gly Thr Thr Ala Ala Ala Ala Gly Ala
325 330 335

Gly Gly Ala Gly Ala Gly Thr Ala Ala Thr Gly Gly Thr Ala Thr Thr
340 345 350

Ala Ala Ala Gly Cys Thr Gly Ala Ala Cys Thr Thr Cys Cys Ala Ala
355 360 365

Ala Thr Cys Thr Thr Gly Ala Ala Gly Ala Ala Gly Ala Gly Cys Thr
370 375 380

Thr Ala Ala Ala Ala Thr Ala Thr Thr Ala Thr Thr Gly Ala Thr Thr
385 390 395 400

Cys Cys Thr Ala Ala Ala Gly Ala Thr Cys Cys Thr Ala Ala Thr Gly
405 410 415

Ala Thr Gly Ala Cys Ala Ala Ala Gly Ala Cys Gly Thr Thr Ala Thr
420 425 430

Thr Gly Thr Ala Gly Ala Ala Ala Thr Ala Ala Gly Ala Gly Cys Ala
435 440 445

Gly Cys Ala Gly Cys Ala Gly Gly Thr Gly Gly Thr Gly Ala Thr Gly
450 455 460

Ala Gly Gly Cys Thr Gly Cys Gly Ala Thr Thr Thr Thr Gly Cys
465 470 475 480

Thr Gly Gly Thr Gly Ala Thr Thr Thr Ala Ala Thr Gly Cys Gly Thr
485 490 495

Ala Thr Gly Thr Ala Thr Thr Cys Ala Ala Ala Gly Thr Ala Thr Gly
500 505 510

Cys Thr Gly Ala Ala Thr Cys Ala Cys Ala Ala Gly Gly Ala Thr Thr
515 520 525

Cys Ala Ala Ala Ala Cys Thr Gly Ala Ala Ala Thr Ala Gly Thr Ala
    530   535   540

Gly Ala Ala Gly Cys Gly Thr Cys Thr Gly Ala Ala Ala Gly Thr Gly
545   550   555   560

Ala Cys Cys Ala Thr Gly Gly Thr Gly Gly Thr Thr Ala Cys Ala Ala
                565   570   575

Ala Gly Ala Ala Ala Thr Thr Ala Gly Thr Thr Thr Cys Thr Cys Ala
            580   585   590

Gly Thr Thr Thr Cys Thr Gly Gly Thr Ala Ala Thr Gly Gly Cys Gly
        595   600   605

Cys Gly Thr Ala Thr Ala Gly Thr Ala Ala Ala Thr Thr Gly Ala Ala
    610   615   620

Ala Thr Thr Thr Gly Ala Ala Ala Ala Thr Gly Gly Thr Gly Cys Gly
625   630   635   640

Cys Ala Cys Cys Gly Cys Gly Thr Thr Cys Ala Ala Cys Gly Thr Gly
                645   650   655

Thr Gly Cys Cys Thr Gly Ala Ala Ala Cys Ala Gly Ala Ala Thr Cys
            660   665   670

Ala Gly Gly Thr Gly Gly Ala Cys Gly Thr Ala Thr Thr Cys Ala Thr
        675   680   685

Ala Cys Thr Thr Cys Ala Ala Cys Ala Gly Cys Thr Ala Cys Ala Gly
    690   695   700

Thr Gly Gly Cys Ala Gly Thr Thr Thr Thr Ala Cys Cys Ala Gly Ala
705   710   715   720

Ala Gly Thr Thr Gly Ala Ala Gly Ala Thr Gly Thr Ala Gly Ala Ala
                725   730   735

Ala Thr Thr Gly Ala Ala Ala Thr Thr Ala Gly Ala Ala Ala Thr Gly
            740   745   750

Ala Ala Gly Ala Thr Thr Thr Ala Ala Ala Ala Ala Thr Cys Gly Ala
        755   760   765

Cys Ala Cys Gly Thr Ala Thr Cys Gly Thr Thr Cys Ala Ala Gly Thr
    770   775   780

Gly Gly Thr Gly Cys Ala Gly Gly Thr Gly Gly Thr Cys Ala Gly Cys
785   790   795   800

Ala Cys Gly Thr Ala Ala Ala Cys Ala Cys Ala Ala Cys Thr Gly Ala
                805   810   815

Cys Thr Cys Thr Gly Cys Ala Gly Thr Ala Cys Gly Thr Ala Thr Thr
            820   825   830

Ala Cys Cys Cys Ala Thr Thr Thr Ala Cys Cys Ala Ala Cys Thr Gly
        835   840   845

Gly Thr Gly Thr Cys Ala Thr Thr Gly Cys Ala Ala Cys Ala Thr Cys

850 855 860

Thr Thr Cys Thr Gly Ala Gly Ala Ala Gly Thr Cys Thr Cys Ala Ala
865 870 875 880

Ala Thr Thr Cys Ala Ala Ala Ala Cys Cys Gly Thr Gly Ala Ala Ala
885 890 895

Ala Ala Gly Cys Ala Ala Thr Gly Ala Ala Ala Gly Thr Gly Thr Thr
900 905 910

Ala Ala Ala Ala Gly Cys Ala Cys Gly Thr Thr Thr Ala Thr Ala Cys
915 920 925

Gly Ala Thr Ala Thr Gly Ala Ala Ala Gly Thr Thr Cys Ala Ala Gly
930 935 940

Ala Ala Gly Ala Ala Cys Ala Ala Cys Ala Ala Ala Ala Gly Thr Ala
945 950 955 960

Thr Gly Cys Gly Thr Cys Ala Cys Ala Ala Cys Gly Thr Ala Ala Ala
965 970 975

Thr Cys Ala Gly Cys Ala Gly Thr Cys Gly Gly Thr Ala Cys Thr Gly
980 985 990

Gly Thr Gly Ala Thr Cys Gly Thr Thr Cys Ala Gly Ala Ala Cys Gly
995 1000 1005

Thr Ala Thr Thr Cys Gly Ala Ala Cys Thr Thr Ala Thr Ala Ala Thr
1010 1015 1020

Thr Ala Thr Cys Cys Ala Cys Ala Ala Ala Gly Cys Cys Gly Thr Gly
1025 1030 1035 1040

Thr Ala Ala Cys Ala Gly Ala Cys Cys Ala Thr Cys Gly Thr Ala Thr
1045 1050 1055

Ala Gly Gly Thr Cys Thr Ala Ala Cys Gly Cys Thr Thr Cys Ala Ala
1060 1065 1070

Ala Ala Ala Thr Thr Ala Gly Gly Gly Cys Ala Ala Ala Thr Thr Ala
1075 1080 1085

Thr Gly Gly Ala Ala Gly Gly Cys Cys Ala Thr Thr Thr Ala Gly Ala
1090 1095 1100

Ala Gly Ala Ala Ala Thr Thr Ala Thr Ala Gly Ala Thr Gly Cys Ala
1105 1110 1115 1120

Cys Thr Gly Ala Cys Thr Thr Thr Ala Thr Cys Ala Gly Ala Gly Cys
1125 1130 1135

Ala Gly Ala Cys Ala Gly Ala Thr Ala Ala Ala Thr Thr Gly Ala Ala
1140 1145 1150

Ala Gly Ala Ala Cys Thr Thr Ala Ala Thr Ala Ala Thr Gly Gly Thr
1155 1160 1165

Gly Ala Ala Thr Thr Ala Thr Ala Ala Ala Gly Ala Ala Ala Ala Gly
1170 1175 1180

Thr Thr Ala Gly Ala Thr Gly Ala Ala Gly Cys Ala Ala Thr Thr Cys
1185 1190 1195 1200

Ala Thr Thr Thr Ala Ala Cys Ala Cys Ala Ala Cys Ala Ala Ala Ala
1205 1210 1215

Ala Gly Gly Gly Thr Thr Thr Gly Ala Ala Cys Ala Ala Ala Cys Ala
1220 1225 1230

Cys Gly Ala Gly Cys Thr Gly Ala Ala Thr Gly Gly Thr Thr Ala Ala
1235 1240 1245

Thr Gly Thr Thr Ala Gly Ala Thr Gly Thr Ala Thr Thr Thr Cys Ala
1250 1255 1260

Ala Thr Gly Gly Ala Cys Gly Cys Gly Thr Ala Cys Gly
1265 1270 1275

<210> 34
<211> 358
<212> PRT
<213> Staphylococcus aureus

<400> 34
Val Phe Asp Gln Leu Asp Ile Val Glu Glu Arg Tyr Glu Gln Leu Asn
1 5 10 15

Glu Leu Leu Ser Asp Pro Asp Val Val Asn Asp Ser Asp Lys Leu Arg
20 25 30

Lys Tyr Ser Lys Glu Gln Ala Asp Leu Gln Lys Thr Val Asp Val Tyr
35 40 45

Arg Asn Tyr Lys Ala Lys Lys Glu Glu Leu Ala Asp Ile Glu Glu Met
50 55 60

Leu Ser Glu Thr Asp Asp Lys Glu Glu Val Glu Met Leu Lys Glu Glu
65 70 75 80

Ser Asn Gly Ile Lys Ala Glu Leu Pro Asn Leu Glu Glu Glu Leu Lys
85 90 95

Ile Leu Leu Ile Pro Lys Asp Pro Asn Asp Asp Lys Asp Val Ile Val
100 105 110

Glu Ile Arg Ala Ala Ala Gly Gly Asp Glu Ala Ala Ile Phe Ala Gly
115 120 125

Asp Leu Met Arg Met Tyr Ser Lys Tyr Ala Glu Ser Gln Gly Phe Lys
130 135 140

Thr Glu Ile Val Glu Ala Ser Glu Ser Asp His Gly Gly Tyr Lys Glu
145 150 155 160

Ile Ser Phe Ser Val Ser Gly Asn Gly Ala Tyr Ser Lys Leu Lys Phe
165 170 175

Glu Asn Gly Ala His Arg Val Gln Arg Val Pro Glu Thr Glu Ser Gly
180 185 190

Gly Arg Ile His Thr Ser Thr Ala Thr Val Ala Val Leu Pro Glu Val
195 200 205

Glu Asp Val Glu Ile Glu Ile Arg Asn Glu Asp Leu Lys Ile Asp Thr
210 215 220

Tyr Arg Ser Ser Gly Ala Gly Gly Gln His Val Asn Thr Thr Asp Ser
225 230 235 240

Ala Val Arg Ile Thr His Leu Pro Thr Gly Val Ile Ala Thr Ser Ser
245 250 255

Glu Lys Ser Gln Ile Gln Asn Arg Glu Lys Ala Met Lys Val Leu Lys
260 265 270

Ala Arg Leu Tyr Asp Met Lys Val Gln Glu Glu Gln Gln Lys Tyr Ala
275 280 285

Ser Gln Arg Lys Ser Ala Val Gly Thr Gly Asp Arg Ser Glu Arg Ile
290 295 300

Arg Thr Tyr Asn Tyr Pro Gln Ser Arg Val Thr Asp His Arg Ile Gly
305 310 315 320

Leu Thr Leu Gln Lys Leu Gly Gln Ile Met Glu Gly His Leu Glu Glu
325 330 335

Ile Ile Asp Ala Leu Thr Leu Ser Glu Gln Thr Asp Lys Leu Lys Glu
340 345 350

Leu Asn Asn Gly Glu Leu
355

<210> 35
<211> 1315
<212> DNA
<213> Staphylococcus aureus

<400> 35
atttcttaac attgttattt aacaaaatta tgttaaaatt tagcattata aaagatgcaa 60
atcaatgact tgaattgaaa tataaatagg agcgaatgct atggaattat cagaaatcaa 120
acgaaatata gataagtata atcaagattt aacacaaatt agggggtctc ttgacttaga 180
gaacaaagaa actaatattc aagaatatga agaaatgatg gcagaaccta atttttggga 240
taaccaaacg aaagcgcaag atattataga taaaaataat gcgttaaaag caatagttaa 300
tggttataaa acactacaag cagaagtaga tgacatggat gctacttggg atttattaca 360
agaagaattt gatgaagaaa tgaaagaaga cttagagcaa gaggtcatta attttaaggc 420
taaagtggat gaatacgaat tgcaattatt attagatggg cctcacgatg ccaataacgc 480
aattctagag ttacatcctg gtgcaggtgg cacggagtct caagattggg ctaatatgct 540
atttagaatg tatcaacgtt attgtgagaa gaaaggcttt aaagttgaaa ctgttgatta 600
tctacctggg gatgaagcgg ggattaaaag tgtaacattg ctcatcaaag ggcataatgc 660
ttatggttat ttaaaagctg aaaaaggtgt acaccgacta gtacgaattt ctccatttga 720
ttcatcagga cgtcgtcata catcatttgc atcatgcgac gttattccag attttaataa 780
tgatgaaata gagattgaaa tcaatccgga tgatattaca gttgatacat tcagagcttc 840
tggtgcaggt ggtcagcata ttaacaaaac tgaatcggca atacgaatta cccaccaccc 900
ctcaggtata gttgttaata accaaaatga acgttctcaa attaaaaacc gtgaagcagc 960
tatgaaaatg ttaaagtcta aattatatca attaaaattg gaagagcagg cacgtgaaat 1020
ggctgaaatt cgtggcgaac aaaaagaaat cggctgggga agccaaatta gatcatatgt 1080
tttccatcca tactcaatgg tgaaagatca tcgtacgaac gaagaaacag gtaaggttga 1140
tgcagtgatg gatggagaca ttggaccatt tatcgaatca tatttaagac agacaatgtc 1200

gcacgattaa tatatatttt aaaaccgagg ctctaaaagg gcgtcggttt ttggtttttt 1260
taaaggtagc taaataaatt gtaaattaga ttttggaata tgatttgttt atgaa 1315

<210> 36
<211> 369
<212> PRT
<213> Staphylococcus aureus

<400> 36
Met Glu Leu Ser Glu Ile Lys Arg Asn Ile Asp Lys Tyr Asn Gln Asp
1 5 10 15

Leu Thr Gln Ile Arg Gly Ser Leu Asp Leu Glu Asn Lys Glu Thr Asn
20 25 30

Ile Gln Glu Tyr Glu Glu Met Met Ala Glu Pro Asn Phe Trp Asp Asn
35 40 45

Gln Thr Lys Ala Gln Asp Ile Ile Asp Lys Asn Asn Ala Leu Lys Ala
50 55 60

Ile Val Asn Gly Tyr Lys Thr Leu Gln Ala Glu Val Asp Asp Met Asp
65 70 75 80

Ala Thr Trp Asp Leu Leu Gln Glu Glu Phe Asp Glu Glu Met Lys Glu
85 90 95

Asp Leu Glu Gln Glu Val Ile Asn Phe Lys Ala Lys Val Asp Glu Tyr
100 105 110

Glu Leu Gln Leu Leu Leu Asp Gly Pro His Asp Ala Asn Asn Ala Ile
115 120 125

Leu Glu Leu His Pro Gly Ala Gly Gly Thr Glu Ser Gln Asp Trp Ala
130 135 140

Asn Met Leu Phe Arg Met Tyr Gln Arg Tyr Cys Glu Lys Lys Gly Phe
145 150 155 160

Lys Val Glu Thr Val Asp Tyr Leu Pro Gly Asp Glu Ala Gly Ile Lys
165 170 175

Ser Val Thr Leu Leu Ile Lys Gly His Asn Ala Tyr Gly Tyr Leu Lys
180 185 190

Ala Glu Lys Gly Val His Arg Leu Val Arg Ile Ser Pro Phe Asp Ser
195 200 205

Ser Gly Arg Arg His Thr Ser Phe Ala Ser Cys Asp Val Ile Pro Asp
210 215 220

Phe Asn Asn Asp Glu Ile Glu Ile Glu Ile Asn Pro Asp Asp Ile Thr
225 230 235 240

Val Asp Thr Phe Arg Ala Ser Gly Ala Gly Gly Gln His Ile Asn Lys
245 250 255

Thr Glu Ser Ala Ile Arg Ile Thr His His Pro Ser Gly Ile Val Val
260 265 270

Asn Asn Gln Asn Glu Arg Ser Gln Ile Lys Asn Arg Glu Ala Ala Met

275 280 285

Lys Met Leu Lys Ser Lys Leu Tyr Gln Leu Lys Leu Glu Glu Gln Ala
290 295 300

Arg Glu Met Ala Glu Ile Arg Gly Glu Gln Lys Glu Ile Gly Trp Gly
305 310 315 320

Ser Gln Ile Arg Ser Tyr Val Phe His Pro Tyr Ser Met Val Lys Asp
325 330 335

His Arg Thr Asn Glu Glu Thr Gly Lys Val Asp Ala Val Met Asp Gly
340 345 350

Asp Ile Gly Pro Phe Ile Glu Ser Tyr Leu Arg Gln Thr Met Ser His
355 360 365

Asp

<210> 37
<211> 840
<212> DNA
<213> Staphylococcus aureus

<400> 37
aataactgaa aatatgatag aattggtaaa tgaatatctg gaaactggaa tgatagttga 60
aggaattaaa aataataaaa ttttagttga ggatgaataa aatgtcagct tttataactt 120
ttgagggccc agaaggctct ggaaaaacaa ctgtaattaa tgaagtttac catagattag 180
taaaagatta tgatgtcatt atgactagag aaccaggtgg tgttcctact ggtgaagaaa 240
tacgtaaaat tgtattagaa ggcaatgata tggacattag aactgaagca atgttatttg 300
ctgcatctag aagagaacat cttgtattaa aggtcatacc agctttaaaa gaaggtaagg 360
ttgtgttgtg tgatcgctat atcgatagtt cattagctta tcaaggttat gctagaggga 420
ttggcgttga agaagtaaga gcattaaacg aatttgcaat aaatggatta tatccagact 480
tgacgattta tttaaatgtt agtgctgaag taggtcgcga acgtattatt aaaaattcaa 540
gagatcaaaa tagattagat caagaagatt taaagtttca cgaaaaagta attgaaggtt 600
accaagaaat cattcataat gaatcacaac ggttcaaaag cgttaatgca gatcaacctc 660
ttgaaaatgt tgttgaagac acgtatcaaa ctatcatcaa atatttagaa aagatatgat 720
ataattgtta gaagaggtgt tataaaatga aaatgattat agcgatcgta caagatcaag 780
atagtcagga acttgcagat caacttgtta aaaataactt tagagcaaca aaattggcaa 840

<210> 38
<211> 205
<212> PRT
<213> Staphylococcus aureus

<400> 38
Met Ser Ala Phe Ile Thr Phe Glu Gly Pro Glu Gly Ser Gly Lys Thr
1 5 10 15

Thr Val Ile Asn Glu Val Tyr His Arg Leu Val Lys Asp Tyr Asp Val
20 25 30

Ile Met Thr Arg Glu Pro Gly Gly Val Pro Thr Gly Glu Glu Ile Arg
35 40 45

Lys Ile Val Leu Glu Gly Asn Asp Met Asp Ile Arg Thr Glu Ala Met
50 55 60

Leu Phe Ala Ala Ser Arg Arg Glu His Leu Val Leu Lys Val Ile Pro

65 70 75 80

Ala Leu Lys Glu Gly Lys Val Val Leu Cys Asp Arg Tyr Ile Asp Ser
85 90 95

Ser Leu Ala Tyr Gln Gly Tyr Ala Arg Gly Ile Gly Val Glu Glu Val
100 105 110

Arg Ala Leu Asn Glu Phe Ala Ile Asn Gly Leu Tyr Pro Asp Leu Thr
115 120 125

Ile Tyr Leu Asn Val Ser Ala Glu Val Gly Arg Glu Arg Ile Ile Lys
130 135 140

Asn Ser Arg Asp Gln Asn Arg Leu Asp Gln Glu Asp Leu Lys Phe His
145 150 155 160

Glu Lys Val Ile Glu Gly Tyr Gln Glu Ile Ile His Asn Glu Ser Gln
165 170 175

Arg Phe Lys Ser Val Asn Ala Asp Gln Pro Leu Glu Asn Val Val Glu
180 185 190

Asp Thr Tyr Gln Thr Ile Ile Lys Tyr Leu Glu Lys Ile
195 200 205

<210> 39
<211> 923
<212> DNA
<213> Staphylococcus aureus

<400> 39
aatgttgctt tattaaaatg taaatcattc taataaaacg acaactgtgt cttctttact 60
tgtatatgtt acatatattc acgatagaga ggataagaaa atggctcaaa tttctaaata 120
taaacgtgta gttttgaaac taagtggtga agcgttagct ggagaaaaag gatttggcat 180
aaatccagta attattaaaa gtgttgctga gcaagtggct gaagttgcta aaatggactg 240
tgaaatcgca gtaatcgttg gtggcggaaa catttggaga ggtaaaacag gtagtgactt 300
aggtatggac cgtggaactg ctgattacat gggtatgctt gcaactgtaa tgaatgcctt 360
agcattacaa gatagtttag aacaattgga ttgtgataca cgagtattaa catctattga 420
aatgaagcaa gtggctgaac cttatattcg tcgtcgtgca attagacact tagaaaagaa 480
acgcgtagtt atttttgctg caggtattgg aaacccatac ttctctacag atactacagc 540
ggcattacgt gctgcagaag ttgaagcaga tgttatttta atgggcaaaa ataatgtaga 600
tggtgtatat tctgcagatc ctaaagtaaa caaagatgcg gtaaaatatg aacatttaac 660
gcatattcaa atgcttcaag aaggtttaca agtaatggat tcaacagcat cctcattctg 720
tatggataat aacattccgt taactgtttt ctctattatg gaagaaggaa atattaaacg 780
tgctgttatg ggtgaaaaga taggtacgtt aattacaaaa taaatttaga ggtgtaaaat 840
aatgagtgac attattaatg aaactaaatc aagaatgcaa aaatcaatcg aaagcttatc 900
acgtgaatta gctaacatca gtg 923

<210> 40
<211> 240
<212> PRT
<213> Staphylococcus aureus

<400> 40
Met Ala Gln Ile Ser Lys Tyr Lys Arg Val Val Leu Lys Leu Ser Gly
1 5 10 15

Glu Ala Leu Ala Gly Glu Lys Gly Phe Gly Ile Asn Pro Val Ile Ile
20 25 30

Lys Ser Val Ala Glu Gln Val Ala Glu Val Ala Lys Met Asp Cys Glu
35 40 45

Ile Ala Val Ile Val Gly Gly Gly Asn Ile Trp Arg Gly Lys Thr Gly
50 55 60

Ser Asp Leu Gly Met Asp Arg Gly Thr Ala Asp Tyr Met Gly Met Leu
65 70 75 80

Ala Thr Val Met Asn Ala Leu Ala Leu Gln Asp Ser Leu Glu Gln Leu
85 90 95

Asp Cys Asp Thr Arg Val Leu Thr Ser Ile Glu Met Lys Gln Val Ala
100 105 110

Glu Pro Tyr Ile Arg Arg Arg Ala Ile Arg His Leu Glu Lys Lys Arg
115 120 125

Val Val Ile Phe Ala Ala Gly Ile Gly Asn Pro Tyr Phe Ser Thr Asp
130 135 140

Thr Thr Ala Ala Leu Arg Ala Ala Glu Val Glu Ala Asp Val Ile Leu
145 150 155 160

Met Gly Lys Asn Asn Val Asp Gly Val Tyr Ser Ala Asp Pro Lys Val
165 170 175

Asn Lys Asp Ala Val Lys Tyr Glu His Leu Thr His Ile Gln Met Leu
180 185 190

Gln Glu Gly Leu Gln Val Met Asp Ser Thr Ala Ser Ser Phe Cys Met
195 200 205

Asp Asn Asn Ile Pro Leu Thr Val Phe Ser Ile Met Glu Glu Gly Asn
210 215 220

Ile Lys Arg Ala Val Met Gly Glu Lys Ile Gly Thr Leu Ile Thr Lys
225 230 235 240

<210> 41
<211> 1013
<212> DNA
<213> Staphylococcus aureus

<400> 41
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tgtacctttt gtttattggt tattggttgg tatcagtatg tggttcttca tcaaccaagg 360
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cccgttatcg ataataccga catatattgt gacaagtaga ttttatggac atttaggctt 480
acttttactt gtgataattg catgtatgtt tactggtatt tatccatcaa tacatatcat 540
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attattttac ttttcaccaa ttttgtggct accaaagaac catggtatca gtggtttaat 720
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agacttcttg taatatattt atatgacgaa accccgctaa ccattaataa atggaagtgg 960
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<210> 42
<211> 270
<212> PRT
<213> Staphylococcus aureus

<400> 42
Met Ser Ala Ile Gly Thr Val Phe Lys Glu His Val Lys Asn Phe Tyr
1 5 10 15

Leu Ile Gln Arg Leu Ala Gln Phe Gln Val Lys Ile Ile Asn His Ser
20 25 30

Asn Tyr Leu Gly Val Ala Trp Glu Leu Ile Asn Pro Val Met Gln Ile
35 40 45

Met Val Tyr Trp Met Val Phe Gly Leu Gly Ile Arg Ser Asn Ala Pro
50 55 60

Ile His Gly Val Pro Phe Val Tyr Trp Leu Leu Val Gly Ile Ser Met
65 70 75 80

Trp Phe Phe Ile Asn Gln Gly Ile Leu Glu Gly Thr Lys Ala Ile Thr
85 90 95

Gln Lys Phe Asn Gln Val Ser Lys Met Asn Phe Pro Leu Ser Ile Ile
100 105 110

Pro Thr Tyr Ile Val Thr Ser Arg Phe Tyr Gly His Leu Gly Leu Leu
115 120 125

Leu Leu Val Ile Ile Ala Cys Met Phe Thr Gly Ile Tyr Pro Ser Ile
130 135 140

His Ile Ile Gln Leu Leu Ile Tyr Val Pro Phe Cys Phe Phe Leu Thr
145 150 155 160

Ala Ser Val Thr Leu Leu Thr Ser Thr Leu Gly Val Leu Val Arg Asp
165 170 175

Thr Gln Met Leu Met Gln Ala Ile Leu Arg Ile Leu Phe Tyr Phe Ser
180 185 190

Pro Ile Leu Trp Leu Pro Lys Asn His Gly Ile Ser Gly Leu Ile His
195 200 205

Glu Met Met Lys Tyr Asn Pro Val Tyr Phe Ile Ala Glu Ser Tyr Arg
210 215 220

Ala Ala Ile Leu Tyr His Glu Trp Tyr Phe Met Asp His Trp Lys Leu
225 230 235 240

Met Leu Tyr Asn Phe Gly Ile Val Ala Ile Phe Phe Ala Ile Gly Ala
245 250 255

Tyr Leu His Met Lys Tyr Arg Asp Gln Phe Ala Asp Phe Leu
260 265 270

<210> 43
<211> 995
<212> DNA
<213> Staphylococcus aureus

<400> 43
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taaaaatgta acaaaagaat atcgtattta tcgtacaaat aaagaacgta tgaaagatgc 180
gctcattccc aaacataaaa acaaaacatt tttcgcttta gatgacatta gtttaaaagc 240
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tattgaattt agtgaacttg gtgagtttat ttatcaacca gttaaaaagt attcaagtgg 540
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acaattttgt actaagattg cttggattga aggcggaaag ttaaaagatt acggtgaact 780
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<210> 44
<211> 264
<212> PRT
<213> Staphylococcus aureus

<400> 44
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Tyr Arg Thr Asn Lys Glu Arg Met Lys Asp Ala Leu Ile Pro Lys His
20 25 30

Lys Asn Lys Thr Phe Phe Ala Leu Asp Asp Ile Ser Leu Lys Ala Tyr
35 40 45

Glu Gly Asp Val Ile Gly Leu Val Gly Ile Asn Gly Ser Gly Lys Ser
50 55 60

Thr Leu Ser Asn Ile Ile Gly Gly Ser Leu Ser Pro Thr Val Gly Lys
65 70 75 80

Val Asp Arg Asn Gly Glu Val Ser Val Ile Ala Ile Ser Ala Gly Leu
85 90 95

Ser Gly Gln Leu Thr Gly Ile Glu Asn Ile Glu Phe Lys Met Leu Cys
100 105 110

Met Gly Phe Lys Arg Lys Glu Ile Lys Ala Met Thr Pro Lys Ile Ile
115 120 125

Glu Phe Ser Glu Leu Gly Glu Phe Ile Tyr Gln Pro Val Lys Lys Tyr
130 135 140

Ser Ser Gly Met Arg Ala Lys Leu Gly Phe Ser Ile Asn Ile Thr Val
145 150 155 160

Asn Pro Asp Ile Leu Val Ile Asp Glu Ala Leu Ser Val Gly Asp Gln
165 170 175

Thr Phe Ala Gln Lys Cys Leu Asp Lys Ile Tyr Glu Phe Lys Glu Gln
180 185 190

Asn Lys Thr Ile Phe Phe Val Ser His Asn Leu Gly Gln Val Arg Gln
195 200 205

Phe Cys Thr Lys Ile Ala Trp Ile Glu Gly Gly Lys Leu Lys Asp Tyr
210 215 220

Gly Glu Leu Asp Asp Val Leu Pro Lys Tyr Glu Ala Phe Leu Asn Asp
225 230 235 240

Phe Lys Lys Lys Ser Lys Ala Glu Gln Lys Glu Phe Arg Asn Lys Leu
245 250 255

Asp Glu Ser Arg Phe Val Ile Lys
260

<210> 45
<211> 738
<212> DNA
<213> Staphylococcus aureus

<400> 45
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aaactggaaa aaatctcgtc gtttaggtat ctctttaagc ggtactggta aagaattaga 180
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tggtttacaa ttacgtgaaa aacaaaaatt acgttactta tatggaatga ctgaaagaca 300
attccgtaac acatttgaca tcgctggtaa aaaattcggt gtacacggtg aaaacttcat 360
gatcttatta gcaagtcgtt tagacgctgt tgtttattca ttaggtttag ctcgtactcg 420
tcgtcaagca cgtcaattag ttaaccacgg tcatatctta gtagatggta aacgtgttga 480
tattccatct tattctgtta aacctggtca aacaatttca gttcgtgaaa aatctcaaaa 540
attaaacatc atcgttgaat cagttgaaat caacaatttc gtacctgagt acttaaactt 600
tgatgctgac agcttaactg gtactttcgt acgtttacca gaacgtagcg aattacctgc 660
tgaaattaac gaacaattaa tccgttgagt actactcaag ataatacggt caataccaac 720
acccacaatt gtgggtgt 738

<210> 46
<211> 195
<212> PRT
<213> Staphylococcus aureus

<400> 46
Met Ala Arg Phe Arg Gly Ser Asn Trp Lys Lys Ser Arg Arg Leu Gly
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Ile Ser Leu Ser Gly Thr Gly Lys Glu Leu Glu Lys Arg Pro Tyr Ala
20 25 30

Pro Gly Gln His Gly Pro Asn Gln Arg Lys Lys Leu Ser Glu Tyr Gly
35 40 45

Leu Gln Leu Arg Glu Lys Gln Lys Leu Arg Tyr Leu Tyr Gly Met Thr

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        50                  55                  60

Glu Arg Gln Phe Arg Asn Thr Phe Asp Ile Ala Gly Lys Lys Phe Gly
65                  70                  75                  80

Val His Gly Glu Asn Phe Met Ile Leu Leu Ala Ser Arg Leu Asp Ala
                85                  90                  95

Val Val Tyr Ser Leu Gly Leu Ala Arg Thr Arg Arg Gln Ala Arg Gln
            100                 105                 110

Leu Val Asn His Gly His Ile Leu Val Asp Gly Lys Arg Val Asp Ile
        115                 120                 125

Pro Ser Tyr Ser Val Lys Pro Gly Gln Thr Ile Ser Val Arg Glu Lys
    130                 135                 140

Ser Gln Lys Leu Asn Ile Ile Val Glu Ser Val Glu Ile Asn Asn Phe
145                 150                 155                 160

Val Pro Glu Tyr Leu Asn Phe Asp Ala Asp Ser Leu Thr Gly Thr Phe
                165                 170                 175

Val Arg Leu Pro Glu Arg Ser Glu Leu Pro Ala Glu Ile Asn Glu Gln
            180                 185                 190

Leu Ile Arg
        195


<210> 47
<211> 980
<212> DNA
<213> Staphylococcus aureus

<400> 47
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caaaatttaa caataaagaa tactagtgag aaatctctta ttaaagggat tgatttgaaa 180
atttttagtc aacagattaa tgccttgatt ggagagagcg gcgctggaaa aagtttgatt 240
gctaaagctt tacttgaata tttaccattt gatttaagct gcacgtatga ttcgtaccaa 300
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tctcaaaatt atgcagaaag ttttaacgac catactaaat taggtaaaca gttaactgcg 420
atttatcgta agcattataa aggtagtaaa gaagaggctt tgtccaaagt tgataaggct 480
ttgtcgtggg ttaatttaca aagcaaagat atattaaata aatatagttt ccaactttct 540
gggggccaac ttgaacgcgt atacatagca agcgttctca tgttggagcc taaattaatc 600
attgcagacg aaccagttgc atcattggat gctttgaacg gtaatcaagt gatggattta 660
ttacagcata ttgtattaga acatggtcaa acattattta ttatcacaca taacttaagt 720
catgtattga aatattgtca gtacatttat gttttaaaag aaggtcaaat cattgaacga 780
ggtaatatta atcatttcaa gtatgagcat ttgcatccgt atactgaacg tctaattaaa 840
tatagaacac aattaaagag ggattactat gattgagtta aaacatgtga cttttggtta 900
taataaaaag cagatggtgc tacaagatat caatattact atacctgatg gagaaaatgt 960
tggtatttta ggcgaaagtg                                              980

<210> 48
<211> 258
<212> PRT
<213> Staphylococcus aureus

<400> 48
Met Met Ser Leu Ile Asp Ile Gln Asn Leu Thr Ile Lys Asn Thr Ser
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            20                  25                  30
Ile Asn Ala Leu Ile Gly Glu Ser Gly Ala Gly Lys Ser Leu Ile Ala
        35                  40                  45
Lys Ala Leu Leu Glu Tyr Leu Pro Phe Asp Leu Ser Cys Thr Tyr Asp
    50                  55                  60
Ser Tyr Gln Phe Asp Gly Glu Asn Val Ser Arg Leu Ser Gln Tyr Tyr
65                  70                  75                  80
Gly His Thr Ile Gly Tyr Ile Ser Gln Asn Tyr Ala Glu Ser Phe Asn
                85                  90                  95
Asp His Thr Lys Leu Gly Lys Gln Leu Thr Ala Ile Tyr Arg Lys His
            100                 105                 110
Tyr Lys Gly Ser Lys Glu Glu Ala Leu Ser Lys Val Asp Lys Ala Leu
        115                 120                 125
Ser Trp Val Asn Leu Gln Ser Lys Asp Ile Leu Asn Lys Tyr Ser Phe
    130                 135                 140
Gln Leu Ser Gly Gly Gln Leu Glu Arg Val Tyr Ile Ala Ser Val Leu
145                 150                 155                 160
Met Leu Glu Pro Lys Leu Ile Ile Ala Asp Glu Pro Val Ala Ser Leu
                165                 170                 175
Asp Ala Leu Asn Gly Asn Gln Val Met Asp Leu Leu Gln His Ile Val
            180                 185                 190
Leu Glu His Gly Gln Thr Leu Phe Ile Ile Thr His Asn Leu Ser His
        195                 200                 205
Val Leu Lys Tyr Cys Gln Tyr Ile Tyr Val Leu Lys Glu Gly Gln Ile
    210                 215                 220
Ile Glu Arg Gly Asn Ile Asn His Phe Lys Tyr Glu His Leu His Pro
225                 230                 235                 240
Tyr Thr Glu Arg Leu Ile Lys Tyr Arg Thr Gln Leu Lys Arg Asp Tyr
                245                 250                 255
Tyr Asp
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<210> 49
<211> 760
<212> DNA
<213> Staphylococcus aureus

<400> 49

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taaaacaggt ttaacaattt ctgttgataa cgctatttgg aaagttatag acttccaaca 180
tgtaaagcct ggtaaaggtt cagcattcgt tcgttcaaaa ttacgtaatt taagaactgg 240
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tgcaattcaa gagaaaacgt ttagagctgg tgaaaaagtt gaaccagcaa tgattgaaaa 300
tcgtcgcatg caatatttat atgctgacgg rgataatcat gtatttatgg ataatgaaag 360
ctttgaacaa acagaacttt caagtgatta cttaaaagaa gaattgaatt acttaaaaga 420
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tgccactaaa tcggcaactg ttgaaactgg ttatacatta aatgtacctt tatttgtaaa 600
cgaaggtgac gttttaatta tcaacactgg tgatggaagc tacatttcaa gaggataatc 660
tctaatttgt taacaaatag cttgtattca ctatactgat ttaacgtaag anattctaaa 720
taagtctcat aaagctattg cctaaaatga ttataggtta 760

<210> 50
<211> 185
<212> PRT
<213> Staphylococcus aureus

<400> 50
Met Ile Ser Val Asn Asp Phe Lys Thr Gly Leu Thr Ile Ser Val Asp
1 5 10 15

Asn Ala Ile Trp Lys Val Ile Asp Phe Gln His Val Lys Pro Gly Lys
20 25 30

Gly Ser Ala Phe Val Arg Ser Lys Leu Arg Asn Leu Arg Thr Gly Ala
35 40 45

Ile Gln Glu Lys Thr Phe Arg Ala Gly Glu Lys Val Glu Pro Ala Met
50 55 60

Ile Glu Asn Arg Arg Met Gln Tyr Leu Tyr Ala Asp Gly Asp Asn His
65 70 75 80

Val Phe Met Asp Asn Glu Ser Phe Glu Gln Thr Glu Leu Ser Ser Asp
85 90 95

Tyr Leu Lys Glu Glu Leu Asn Tyr Leu Lys Glu Gly Met Glu Val Gln
100 105 110

Ile Gln Thr Tyr Glu Gly Glu Thr Ile Gly Val Glu Leu Pro Lys Thr
115 120 125

Val Glu Leu Thr Val Thr Glu Thr Glu Pro Gly Ile Lys Gly Asp Thr
130 135 140

Ala Thr Gly Ala Thr Lys Ser Ala Thr Val Glu Thr Gly Tyr Thr Leu
145 150 155 160

Asn Val Pro Leu Phe Val Asn Glu Gly Asp Val Leu Ile Ile Asn Thr
165 170 175

Gly Asp Gly Ser Tyr Ile Ser Arg Gly
180 185

<210> 51
<211> 9326
<212> DNA
<213> Staphylococcus aureus

<400> 51
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<210> 52
<211> 981
<212> DNA
<213> Staphylococcus aureus

<400> 52
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cgagaaaata ttaaaagttt ggctgacgat catgtgtttg aattagatat tcgtgaatat 180
gatgcagttg aacaaatcat gaagacatat caatttgatt atgttattca tttagcagca 240
ttagttagtg ttgctgagtc ggttgagaaa cctatcttat ctcaagaaat aaacgtcgta 300
gcaacattaa gattgttaga aatcattaaa aaatataata atcatataaa acgttttatc 360
tttgcttcgt cagcagctgt ttatggtgat cttcctgatt tgcctaaaag tgatcaatca 420
ttaatcttac cattatcacc atatgcaata gataaatatt acggcgaacg gacgacatta 480
aattattgtt cgttatataa cataccaaca gcggttgtta aattttttaa tgtatttggg 540
ccaagacagg atcctaagtc acaatattca ggtgtgattt caaagatgtt cgattcattt 600
gagcataaca agccatttac atttttggt gacggactgc aaactagaga ttttgtatat 660
gtatatgatg ttgttcaatc tgtacgctta attatggaac acaaagatgc aattggacac 720
ggttataaca ttggtacagg cacttttact aatttattag aggtttatcg tattattggt 780
gaattatatg gaaaatcagt cgagcatgaa tttaaagaag cacgaaaagg agatattaag 840
cattcttatg cagatatttc taacttaaag gcattaggat ttgttcctaa atatacagta 900
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<210> 53
<211> 326
<212> PRT
<213> Staphylococcus aureus

<400> 53
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Gly Ser His Leu Val Asp Asp Leu Gln Gln Asp Tyr Asp Val Tyr Val
20 25 30

Leu Asp Asn Tyr Arg Thr Gly Lys Arg Glu Asn Ile Lys Ser Leu Ala
35 40 45

Asp Asp His Val Phe Glu Leu Asp Ile Arg Glu Tyr Asp Ala Val Glu
50 55 60

Gln Ile Met Lys Thr Tyr Gln Phe Asp Tyr Val Ile His Leu Ala Ala
65 70 75 80

Leu Val Ser Val Ala Glu Ser Val Glu Lys Pro Ile Leu Ser Gln Glu
85 90 95

Ile Asn Val Val Ala Thr Leu Arg Leu Leu Glu Ile Ile Lys Lys Tyr
100 105 110

Asn Asn His Ile Lys Arg Phe Ile Phe Ala Ser Ser Ala Ala Val Tyr
115 120 125

Gly Asp Leu Pro Asp Leu Pro Lys Ser Asp Gln Ser Leu Ile Leu Pro
130 135 140

Leu Ser Pro Tyr Ala Ile Asp Lys Tyr Tyr Gly Glu Arg Thr Thr Leu
145 150 155 160

Asn Tyr Cys Ser Leu Tyr Asn Ile Pro Thr Ala Val Val Lys Phe Phe
165 170 175

Asn Val Phe Gly Pro Arg Gln Asp Pro Lys Ser Gln Tyr Ser Gly Val
180 185 190

Ile Ser Lys Met Phe Asp Ser Phe Glu His Asn Lys Pro Phe Thr Phe
195 200 205

Phe Gly Asp Gly Leu Gln Thr Arg Asp Phe Val Tyr Val Tyr Asp Val
210 215 220

Val Gln Ser Val Arg Leu Ile Met Glu His Lys Asp Ala Ile Gly His
225 230 235 240

Gly Tyr Asn Ile Gly Thr Gly Thr Phe Thr Asn Leu Leu Glu Val Tyr
245 250 255

Arg Ile Ile Gly Glu Leu Tyr Gly Lys Ser Val Glu His Glu Phe Lys
260 265 270

Glu Ala Arg Lys Gly Asp Ile Lys His Ser Tyr Ala Asp Ile Ser Asn
275 280 285

Leu Lys Ala Leu Gly Phe Val Pro Lys Tyr Thr Val Glu Thr Gly Leu
290 295 300

Lys Asp Tyr Phe Asn Phe Glu Val Asp Asn Ile Glu Glu Val Thr Ala
305 310 315 320

Lys Glu Val Glu Met Ser
325

<210> 54
<211> 504
<212> DNA
<213> Staphylococcus aureus

<400> 54
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aacgcagaga aaaacggtgc gcaatgggct gataaagatg atgatcgtat aacaaatgtc 180
gggaagttta ttcgtaaaac acgcattgat gaattaccac aactaattaa tgttgttaaa 240
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tcagaagtga taggtttcga gcaaagatgt cttgttacac cagggttaac aggacttgcg 360
caaattcaag gtggatatga cttaacaccg caacaaaaac tgaaatatga catgaaatat 420
atacataaag gtagtttaat gatggaacta tatatatcaa ttagaacatt gatggttgtt 480
attacagggg aaggctcaag gtag 504

<210> 55
<211> 200
<212> PRT
<213> Staphylococcus aureus

<400> 55
Leu Asp Lys Leu Glu Glu Val Arg Lys Ser Tyr Tyr Pro Ile Lys Arg
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Ala Ile Asp Leu Ile Leu Ser Ile Val Leu Leu Phe Leu Thr Leu Pro
20 25 30

Ile Met Val Ile Phe Ala Ile Ala Ile Val Ile Asp Ser Pro Gly Asn
35 40 45

Pro Ile Tyr Ser Gln Val Arg Val Gly Lys Met Gly Lys Leu Ile Lys
50 55 60

Ile Tyr Lys Leu Arg Ser Met Cys Lys Asn Ala Glu Lys Asn Gly Ala
65 70 75 80

Gln Trp Ala Asp Lys Asp Asp Asp Arg Ile Thr Asn Val Gly Lys Phe
85 90 95

Ile Arg Lys Thr Arg Ile Asp Glu Leu Pro Gln Leu Ile Asn Val Val
100 105 110

Lys Gly Glu Met Ser Phe Ile Gly Pro Arg Pro Glu Arg Pro Glu Phe
115 120 125

Val Glu Leu Phe Ser Ser Glu Val Ile Gly Phe Glu Gln Arg Cys Leu
130 135 140

Val Thr Pro Gly Leu Thr Gly Leu Ala Gln Ile Gln Gly Gly Tyr Asp
145 150 155 160

Leu Thr Pro Gln Gln Lys Leu Lys Tyr Asp Met Lys Tyr Ile His Lys
165 170 175

Gly Ser Leu Met Met Glu Leu Tyr Ile Ser Ile Arg Thr Leu Met Val

180 185 190

Val Ile Thr Gly Glu Gly Ser Arg
195 200

<210> 56
<211> 1044
<212> DNA
<213> Staphylococcus aureus

<400> 56
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aaacctgatg ttatccattt acattcttcc aaagctggaa cggtcggacg aattgcgaag 180
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tttaatcgat tgaaattaac cacaatacat aatggtattg cagatgttcc cgctgttaag 420
caaacgctaa aaagccaatc acataacaat attggcgaag tagttggaat gttgcctaat 480
aaacaagatt tacagattaa tgccccgaca aagcatcaat ttgttatgat tgcaagattt 540
gcttatccaa aattgccaca aaatctaatc gcggcaatag agatattgaa attacataac 600
agtaatcatg cgcattttac atttataggc gatggaccta cattaaatga ttgtcagcaa 660
caagttgtac aagctgggtt agaaaatgat gtcacatttt tgggcaatgt cattaatgcg 720
agtcatttat tatcacaata cgatacgttt attttaataa gtaagcatga aggtttgcca 780
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gctaaagtcc tggaaaaata tttaatagac agtgattaca tcaaaatgag taatcaatct 960
agaaaacgtt atttagaatg ttttactgag gagaaaatga ttaaagaagt ggaagacgtt 1020
tataatggaa aatcaacaca atag 1044

<210> 57
<211> 388
<212> PRT
<213> Staphylococcus aureus

<400> 57
Leu Lys Ile Ile Tyr Cys Ile Thr Lys Ala Asp Asn Gly Gly Ala Gln
1 5 10 15

Thr His Leu Ile Gln Leu Ala Asn His Phe Cys Val His Asn Asp Val
20 25 30

Tyr Val Ile Val Gly Asn His Gly Pro Met Ile Glu Gln Leu Asp Ala
35 40 45

Arg Val Asn Val Ile Ile Ile Glu His Leu Val Gly Pro Ile Asp Phe
50 55 60

Lys Gln Asp Ile Leu Ala Val Lys Val Leu Ala Gln Leu Phe Ser Lys
65 70 75 80

Ile Lys Pro Asp Val Ile His Leu His Ser Ser Lys Ala Gly Thr Val
85 90 95

Gly Arg Ile Ala Lys Phe Ile Ser Lys Ser Lys Asp Thr Arg Ile Val
100 105 110

Phe Thr Ala His Gly Trp Ala Phe Thr Glu Gly Val Lys Pro Ala Lys
115 120 125

Lys Phe Leu Tyr Leu Val Ile Glu Lys Leu Met Ser Leu Ile Thr Asp
130 135 140

Ser Ile Ile Cys Val Ser Asp Phe Asp Lys Gln Leu Ala Leu Lys Tyr
145 150 155 160

Arg Phe Asn Arg Leu Lys Leu Thr Thr Ile His Asn Gly Ile Ala Asp
165 170 175

Val Pro Ala Val Lys Gln Thr Leu Lys Ser Gln Ser His Asn Asn Ile
180 185 190

Gly Glu Val Val Gly Met Leu Pro Asn Lys Gln Asp Leu Gln Ile Asn
195 200 205

Ala Pro Thr Lys His Gln Phe Val Met Ile Ala Arg Phe Ala Tyr Pro
210 215 220

Lys Leu Pro Gln Asn Leu Ile Ala Ala Ile Glu Ile Leu Lys Leu His
225 230 235 240

Asn Ser Asn His Ala His Phe Thr Phe Ile Gly Asp Gly Pro Thr Leu
245 250 255

Asn Asp Cys Gln Gln Gln Val Val Gln Ala Gly Leu Glu Asn Asp Val
260 265 270

Thr Phe Leu Gly Asn Val Ile Asn Ala Ser His Leu Leu Ser Gln Tyr
275 280 285

Asp Thr Phe Ile Leu Ile Ser Lys His Glu Gly Leu Pro Ile Ser Ile
290 295 300

Ile Glu Ala Met Ala Thr Gly Leu Pro Val Ile Ala Ser His Val Gly
305 310 315 320

Gly Ile Ser Glu Leu Val Ala Asp Asn Gly Ile Cys Met Met Asn Asn
325 330 335

Gln Pro Glu Thr Ile Ala Lys Val Leu Glu Lys Tyr Leu Ile Asp Ser
340 345 350

Asp Tyr Ile Lys Met Ser Asn Gln Ser Arg Lys Arg Tyr Leu Glu Cys
355 360 365

Phe Thr Glu Glu Lys Met Ile Lys Glu Val Glu Asp Val Tyr Asn Gly
370 375 380

Lys Ser Thr Gln
385

<210> 58
<211> 1239
<212> DNA
<213> Staphylococcus aureus

<400> 58
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ctaatattag tttatttact gtttttcgct aaccatttat taaaggcaaa tcatttttta 180

cagtttttca ttattttgta tacatatcgt atgattatta cgctttgttt gctatttttt 240
gatgatttga tatttattac ggttaaggaa gttcttgcat ctacagttaa atatgcattt 300
gtagtcattt atttctattt agggatgatc atctttaagt taggtaatag caaaaaagtg 360
atcgttacct cttatattat aagcagtgtg actataggtc tattttgtat tatagctggt 420
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aagtatattc ataattacat attcaaggtc cttgcatgtg gtattttgct atggtcttta 600
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caatatgaaa agatggaaag ggatcgtaat gaagagtga 1239

<210> 59
<211> 412
<212> PRT
<213> Staphylococcus aureus

<400> 59
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Leu Ala Val Phe Ile Gln Gln Ser Ser Val Ile Ala Gly Val Asn Val
20 25 30

Ser Ile Ala Asp Phe Ile Thr Leu Leu Ile Leu Val Tyr Leu Leu Phe
35 40 45

Phe Ala Asn His Leu Leu Lys Ala Asn His Phe Leu Gln Phe Phe Ile
50 55 60

Ile Leu Tyr Thr Tyr Arg Met Ile Ile Thr Leu Cys Leu Leu Phe Phe
65 70 75 80

Asp Asp Leu Ile Phe Ile Thr Val Lys Glu Val Leu Ala Ser Thr Val
85 90 95

Lys Tyr Ala Phe Val Val Ile Tyr Phe Tyr Leu Gly Met Ile Ile Phe
100 105 110

Lys Leu Gly Asn Ser Lys Lys Val Ile Val Thr Ser Tyr Ile Ile Ser
115 120 125

Ser Val Thr Ile Gly Leu Phe Cys Ile Ile Ala Gly Leu Asn Lys Ser
130 135 140

Pro Leu Leu Met Lys Leu Leu Tyr Phe Asp Glu Ile Arg Ser Lys Gly
145 150 155 160

Leu Met Asn Asp Pro Asn Tyr Phe Ala Met Thr Gln Ile Ile Thr Leu
165 170 175

Val Leu Ala Tyr Lys Tyr Ile His Asn Tyr Ile Phe Lys Val Leu Ala
180 185 190

Cys Gly Ile Leu Leu Trp Ser Leu Thr Thr Thr Gly Ser Lys Thr Ala
195 200 205

Phe Ile Ile Leu Ile Val Leu Ala Ile Tyr Phe Phe Ile Lys Lys Leu
210 215 220

Phe Ser Arg Asn Ala Val Ser Val Val Ser Met Ser Val Ile Met Leu
225 230 235 240

Ile Leu Leu Cys Phe Thr Phe Tyr Asn Ile Asn Tyr Tyr Leu Phe Gln
245 250 255

Leu Ser Asp Leu Asp Ala Leu Pro Ser Leu Asp Arg Met Ala Ser Ile
260 265 270

Phe Glu Glu Gly Phe Ala Ser Leu Asn Asp Ser Gly Ser Glu Arg Ser
275 280 285

Val Val Trp Ile Asn Ala Ile Ser Val Ile Lys Tyr Thr Leu Gly Phe
290 295 300

Gly Val Gly Leu Val Asp Tyr Val His Ile Gly Ser Gln Ile Asn Gly
305 310 315 320

Ile Leu Leu Val Ala His Asn Thr Tyr Leu Gln Ile Phe Ala Glu Trp
325 330 335

Gly Ile Leu Phe Gly Ala Leu Phe Ile Ile Phe Met Leu Tyr Leu Leu
340 345 350

Phe Glu Leu Phe Arg Phe Asn Ile Ser Gly Lys Asn Val Thr Ala Ile
355 360 365

Val Val Met Leu Thr Met Leu Ile Tyr Phe Leu Thr Val Ser Phe Asn
370 375 380

Asn Ser Arg Tyr Val Ala Phe Ile Leu Gly Ile Ile Val Phe Ile Val
385 390 395 400

Gln Tyr Glu Lys Met Glu Arg Asp Arg Asn Glu Glu
405 410

<210> 60
<211> 1455
<212> DNA
<213> Staphylococcus aureus

<400> 60
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cgtgcatttg gtcccagtgg tgtgggtatt gtttcatttt ctttcaatat cgtgcaatac 180
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gcatacttat taccaaatgg acagctcaac ttatatacta gtatttcttg cgttgttctt 720

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cataaaacaa tttaa                                                  1455
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<210> 61
<211> 476
<212> PRT
<213> Staphylococcus aureus

<400> 61

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Gln Leu Ile Arg Thr Met Thr Pro Leu Ile Thr Ile Pro Ile Ile Ser
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Arg Ala Phe Gly Pro Ser Gly Val Gly Ile Val Ser Phe Ser Phe Asn
        35                  40                  45

Ile Val Gln Tyr Phe Leu Met Ile Ala Ser Val Gly Val Gln Leu Tyr
    50                  55                  60

Phe Asn Arg Val Ile Ala Lys Ser Val Asn Asp Lys Arg Gln Leu Ser
65                  70                  75                  80

Gln Gln Phe Trp Asp Ile Phe Val Ser Lys Leu Phe Leu Ala Leu Thr
                85                  90                  95

Val Phe Ala Met Tyr Met Val Val Ile Thr Ile Phe Ile Asp Asp Tyr
            100                 105                 110

Tyr Leu Ile Phe Leu Leu Gln Gly Ile Tyr Ile Ile Gly Ala Ala Leu
        115                 120                 125

Asp Ile Ser Trp Phe Tyr Ala Gly Thr Glu Lys Phe Lys Ile Pro Ser
    130                 135                 140

Leu Ser Asn Ile Val Ala Ser Gly Ile Val Leu Ser Val Val Val Ile
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Phe Val Lys Asp Gln Ser Asp Leu Ser Leu Tyr Val Phe Thr Ile Ala
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Ile Val Thr Val Leu Asn Gln Leu Pro Leu Phe Ile Tyr Leu Lys Arg
            180                 185                 190

Tyr Ile Ser Phe Val Ser Val Asn Trp Ile His Val Trp Gln Leu Phe
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Arg Ser Ser Leu Ala Tyr Leu Leu Pro Asn Gly Gln Leu Asn Leu Tyr
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Thr Ser Ile Ser Cys Val Val Leu Gly Leu Val Gly Thr Tyr Gln Gln
225 230 235 240

Val Gly Ile Phe Ser Asn Ala Phe Asn Ile Leu Thr Val Ala Ile Ile
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Met Ile Asn Thr Phe Asp Leu Val Met Ile Pro Arg Ile Thr Lys Met
260 265 270

Ser Ile Gln Gln Ser His Ser Leu Thr Lys Thr Leu Ala Asn Asn Met
275 280 285

Asn Ile Gln Leu Ile Leu Thr Ile Pro Met Val Phe Gly Leu Ile Ala
290 295 300

Ile Met Pro Ser Phe Tyr Leu Trp Phe Phe Gly Glu Glu Phe Ala Ser
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Thr Val Pro Leu Met Thr Ile Leu Ala Ile Leu Val Leu Ile Ile Pro
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Leu Asn Met Leu Ile Ser Arg Gln Tyr Leu Leu Ile Val Asn Lys Ile
340 345 350

Arg Leu Tyr Asn Ala Ser Ile Thr Ile Gly Ala Val Ile Asn Leu Val
355 360 365

Leu Cys Ile Ile Leu Ile Tyr Phe Tyr Gly Ile Tyr Gly Ala Ala Ile
370 375 380

Ala Arg Leu Ile Thr Glu Phe Phe Leu Leu Ile Trp Arg Phe Ile Asp
385 390 395 400

Ile Thr Lys Ile Asn Val Lys Leu Asn Ile Val Ser Thr Ile Gln Cys
405 410 415

Val Ile Ala Ala Val Met Met Phe Ile Val Leu Gly Val Val Asn His
420 425 430

Tyr Leu Pro Pro Thr Met Tyr Ala Thr Leu Leu Leu Ile Ala Ile Gly
435 440 445

Ile Val Val Tyr Leu Leu Leu Met Met Thr Met Lys Asn Gln Tyr Val
450 455 460

Trp Gln Ile Leu Arg His Leu Arg His Lys Thr Ile
465 470 475

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A3

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Published
With international search report.

(88) Date of publication of the international search report: 15 June 2000 (15.06.00)

(54) Title: *STAPHYLOCOCCUS AUREUS* GENES AND POLYPEPTIDES

(57) Abstract

The present invention relates to novel genes from *S. aureus* and the polypeptides they encode. Also provided are vectors, host cells, antibodies and recombinant methods for producing the same. The invention further relates to screening methods for identifying agonists and antagonists of *S. aureus* polypetide activity. The invention additionally relates to diagnostic methods for detecting *Staphylococcus* nucleic acids, polypeptides and antibodies in a biological sample. The present invention further relates to novel vaccines for the prevention or attenuation of infection by *Staphylococcus*.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19726

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :C12N 15/31,15/66, 15/63, 1/21: C07K 14/31
US CL :536/23.7; 435/91.41, 320.1, 252.3, 69.1; 530/350
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.7; 435/91.41, 320.1, 252.3, 69.1; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Genbank, Swissprot, PIR60, SPTREMBL9
search terms: sequences corresponding to SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 843 016 A2 (SMITHKLINE BEECHAM CORPORATION) 20 May 1998, page 23 (relevant to instant SEQ ID NO:16).	1-11
X	EP 0 811 696 A2 (SMITHKINE BEECHAM CORPORATION) 10 December 1997, page 8 (relevant to instant SEQ ID NO: 12).	1-11
X	EP 0 826 774 A2 (SMITHKINE BEECHAM CORPORATION) 14 March 1998, Figure 1 (relevant to instant SEQ ID NO: 6).	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 FEBRUARY 2000	06 APR 2000

Name and mailing address of the ISA/US
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19726

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-11

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19726

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-11, drawn to Staphylococcal nucleic acids, proteins encoded by the nucleic acids, vectors comprising the nucleic acids, methods of making the vectors, cells comprising the vectors, and methods of expressing the nucleic acids in transformed cells.
Group II, claim(s) 12 and 13, drawn to an antibody and a cell producing an antibody, both antibodies being specific for the protein encoded by the nucleic acids of Group I.
Group III, claim(s) 16, drawn to a vaccine comprising a protein encoded by the nucleic acids of Group I.
Group IV, claim(s)17, drawn to a method of preventing an infection by administration of a protein encoded by the nucleic acids of Group I.
Group V, claim(s) 18, drawn to a Staphylococcal nucleic acid assay using the nucleic acids of Group I as probes.
Group VI, claim(s) 19, drawn to an assay of antibodies specific for Staphylococcal proteins using proteins encoded by the nucleic acids of Group I.
Group VII, claim 20, drawn to an assay of the Staphylococcal proteins of Group I using antibodies specific for the proteins of Group I.

The inventions listed as Groups I-VII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Groups II-VII constitute the third product, and the second through fifth methods of use of the products of Group I. PCT Rule 13.1 and Annex B do not show that unity of invention exists between a first and second product or method of use.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

The amino acid sequences of the polypeptides shown in Table 1.

The claims are deemed to correspond to the species listed above in the following manner:

All claims of each Group discussed above are drawn to the species indicated above.

The following claims are generic: Claims 1-20

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Each species is drawn to a different amino acid sequence, and to nucleic acids encoding different amino acid sequences. There is no disclosed relationship between the sequences of each individual species disclosed in Table 1.

Restriction to a single species has been waived sua sponte and the Applicants are permitted to have ten species examined without payment of additional fees. The Applicant's representative Kenley Hoover elected telephonically on 1/27/00 to have the sequences corresponding to SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 examined.